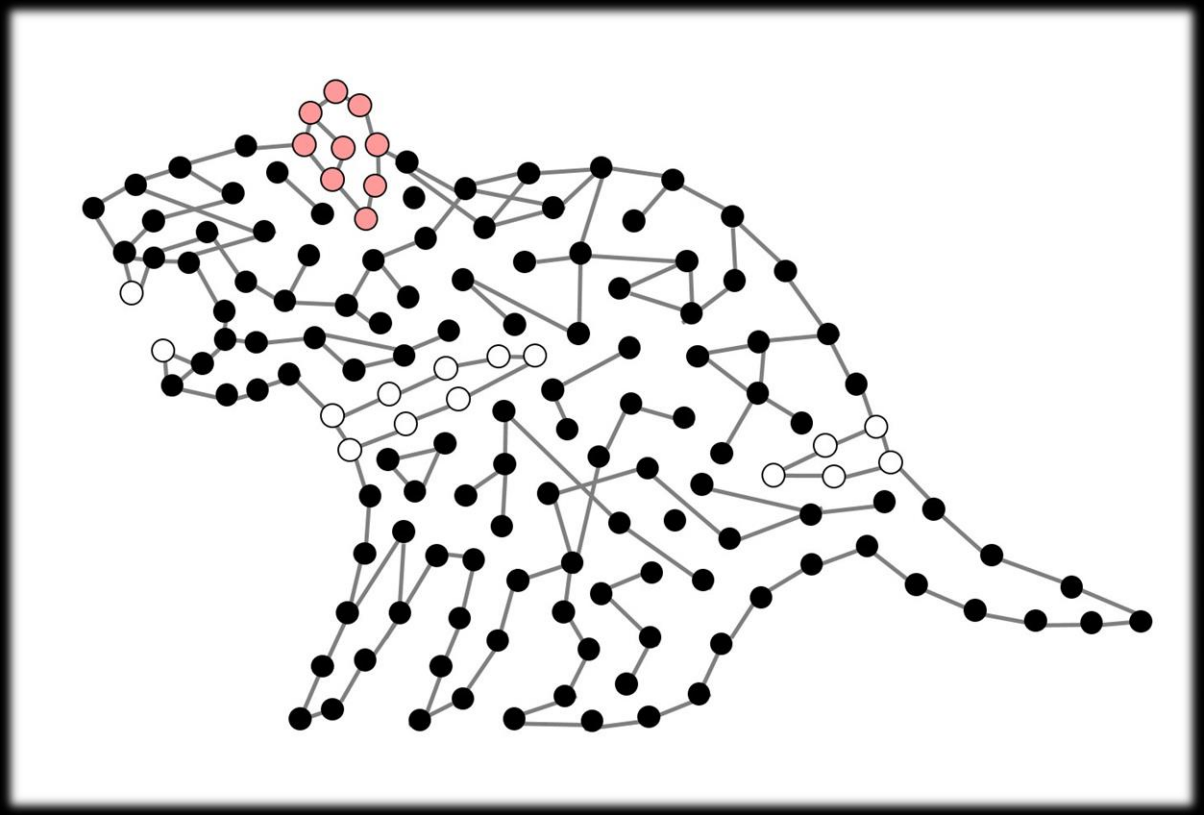
UNIVERSITY of TASMANIA

FACULTY OF SCIENCE, ENGINEERING AND TECHNOLOGY

Behaviour, social networks and transmission of devil facial tumour disease



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Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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Declarations by the Author

Declaration of originality

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The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

All wildlife research carried out by the candidate was conducted with approval from the University of Tasmania Animal Ethics Committee (Approval N^{o}s: A13326, A15835) and the Department of Primary Industries, Parks, Water and Environment (Permit N^{o}s: TFA14228, TFA16180, TFA18028).

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This project was undertaken with approval from the University of Tasmania Ethics Committee (Approval N^{o}s: A13326, A15835), the Department of Primary Industries, Parks, Water and the Environment (Permit N^{o}s: TFA14228, TFA16180, TFA18028) and Sustainable Timber Tasmania (Permit N^{o}: 1505).

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Statement of co-authorship and contribution

Published work produced as part of this thesis:

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Rodrigo Hamede	Greg Jordan
(Candidate's supervisor)	(Head of School)

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* In life. Though, of course, I'd also recommend reading on to Chapter 1!

Abstract

Behavioural processes are key to our understanding of the transmission of infectious diseases in wildlife. The way an animal interacts with its conspecifics and the environment around it, impacts its likelihood of acquiring and transmitting infection. However, behavioural influences are often overlooked in disease ecology. In the case of oncogenic phenomena, despite their ubiquity across taxonomic groups, studies that integrate behaviour and cancer are rare. Tasmanian devils (*Sarcophilus harrisii*) present a unique study system to examine the influences of behaviour on cancer, and vice versa. For more than two decades, devils have been affected by devil facial tumour disease (DFTD), a transmissible cancer in which tumours can be observed and diagnosed externally. Transmission of DFTD is driven by aggressive interactions between devils, when susceptible and infected individuals bite one another. Studying behavioural variation during epidemics and evaluating how infection status affects the likelihood of becoming involved in the transmission process are crucial aspects for understanding individual and population-level dynamics of the disease.

In this thesis I first investigate patterns in devil behaviour, concentrating on their response to handling, at the local scale and with increasing time since DFTD outbreak. By investigating large datasets collected from different populations across Tasmania, I found that devils are relatively flexible in the behaviours they display towards a novel stimulus. This flexibility suggests that there is scope for behavioural responses to reduce the likelihood of becoming infected. Additionally, I found an overall pattern of decline in responsiveness with increasing time since DFTD outbreak. Such a pattern suggests that DFTD is exerting a selective

pressure on reactive devils, highlighting the importance of behaviour to the transmission process.

To further investigate behavioural influences on transmission dynamics, I looked at how devil's contact patterns influence likelihood of involvement in potential transmission events. I fitted an adult population of devils with proximity logging radio-collars to constantly monitor their interactions, while simultaneously recording their accrual of bite wounds via regular captures. I established that males are particularly vulnerable to accruing high numbers of bite wounds during extended mating season interactions with females. This pattern could be an important driver of disease dynamics in devil populations, and I discuss these implications for the transmission process and lack of sex bias observed in DFTD infection rates. Then I used the contact pattern and bite wound data to simulate disease outbreaks through the collared devil population using a network modelling framework. Divergences in epidemiological predictions were evaluated using network models based on a) contacts alone (contact networks) and b) those based solely on bite wounds as potential transmission events (transmission networks). Contact network-based models produced highly inflated values for critical epidemiological parameters compared to those produced using transmission networks. Additionally, seasonal interaction patterns were strong drivers of infection, though not enough to sustain an epidemic in isolation. Predictions made on accurate transmission networks are rare in disease ecology. My study system and results provide a good opportunity to evaluate the type of data required to parametrise epidemiological models and the efficacy of interventions and management strategies.

Having established the potential for DFTD to spread through a naïve devil population, I investigated actual spread through a recently infected population by fitting proximity loggers and recording contact patterns, bite wound accrual and disease status. This detailed dataset allowed me to evaluate whether individual's interactions and role within their social network alter upon DFTD infection. DFTD had significant effects on interaction patterns as infection progressed, while no clear link was found between network position and the probability of infection. This is the first study to investigate the early stages of a local DFTD outbreak in detail, and document how infection status influences behavioural patterns.

This set of studies provides a novel and integrative approach to understand the behavioural responses of a nocturnal and cryptic species throughout different epidemic stages of a transmissible cancer. Furthermore, I provide qualitative and quantitative assessments of individual behaviour across contact networks and assess their influence on the probability of acquiring infection. This information can be used to assist ongoing management strategies to mitigate the effects of DFTD in the wild. Integrating behavioural studies (using novel technologies such as proximity loggers) into mainstream disease ecology will greatly improve our understanding of disease transmission processes in wild animal populations. The insights generated from this thesis have broad applications in the fields of animal behaviour, epidemiology, disease ecology and conservation biology.

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Chapter 1

General Introduction: Behaviour in the context of social networks, Tasmanian devils and DFTD

Animal behaviour

Behaviour is a critical biological process, representing the interface of an animal with its environment. The way in which animals interact with conspecifics, the ecosystem where they live and processes flowing through it, have important consequences at the individual level. These include traits that impact natural selection, ranging from longevity (Stamps 2007) to likelihood of successfully reproducing (Patrick and Weimerskirch 2015; Bubac et al. 2018). At the population level, individual behaviours can have a variety of impacts, including on social structure, predation rates or vulnerability to invasion by novel pathogens (Wolf and Weissing 2012). As a result, behaviour and its consequences have an important role in the structure and functioning of animal societies (Brakes et al. 2019). Studying the nature of animal interactions and their knock-on effects can greatly advance our understanding of ecology on a broader scale.

Despite its key role within ecosystems, the subtleties of individual behavioural differences can be overlooked in biological studies. In many cases, a broader population-level lens is taken, sometimes with the inherent assumption that individuals behave in a homogenous fashion (Dall et al. 2004). Depending on the precise focus of the study, this can be valid, but it misses the key role that social relationships can play in population ecology. Incorporating the heterogeneities and influences of behaviour on ecological studies has improved our strategies toward various landscape-scale management issues, from the spread of disease (McDonald et al. 2018) to targeted reintroductions (Buchholz 2007). The key to the successful integration of behavioural knowledge into studies looking beyond the individual, is understanding the social relationships between animals and how these translate to the population as a whole. This can be achieved by viewing and studying populations as

interconnected individuals within a social network, structured by the interactions occurring between them.

Social Network Analysis

Social networks and their implications for divergent population-level metrics have been studied since the 1930s, but were initially restricted to the fields of mathematics and sociology (Borgatti et al. 2009; Borgatti et al. 2013). Social network analysis (SNA) examines the discrete components which make up systems, while simultaneously allowing investigation of how they interact together within, and between, divergent systems (Wasserman and Faust 1994). As a result, SNA represents a relevant, accessible approach which is useful in fields ranging from pure mathematics and electrical engineering (Scott 1988; Wellman 2008) to biological systems (May 2006). However, the use of SNA in the field of animal behaviour and disease ecology is relatively recent, though it has been burgeoning for the last decade or so (Krause et al. 2009; Krause et al. 2014).

In its most basic form, a social network can be defined as any number of units linked together through social ties. Depending on the field, these units can represent any hierarchical level, including genes, individuals, groups of individuals, communities, species, institutions or even concepts (Proulx *et al.* 2005). In SNA, network units are commonly referred to as nodes. Networks are linked together by edges, which describe interactions between nodes. These edges can depict divergent forms of interaction depending on the type of network; for example, an edge can denote basic contact between individuals, or a more specific type of contact such as sexual or aggressive interactions. Additionally, edges can represent slightly different facets such as transfer of commodities, energy, information or disease (Christian et

al. 2005; Isaac et al. 2007; Cauchemez et al. 2011; Allen et al. 2013; Aplin et al. 2015). Edges can be weighted, representing the strength (or frequency) of interaction between nodes, and/or directed for interactions with a clear instigator and recipient (e.g. the instigation of aggressive interactions or grooming). As an example, Figure 1.1 illustrates allopreening interactions within a small population of birds. Each individual within the network is represented by a small numbered diagram, while arrows between them convey the instigation of preening interactions. The thickness of the arrows indicates how regularly two individuals preen one another, while the direction of the arrow indicates the instigator and receiver of preening. This is a basic network representation, but larger, more complex networks encompassing a variety of different relationships can allow examination of complex social structures, interactions and commodity transfer within large populations (Wey et al. 2008; Farine and Whitehead 2015).

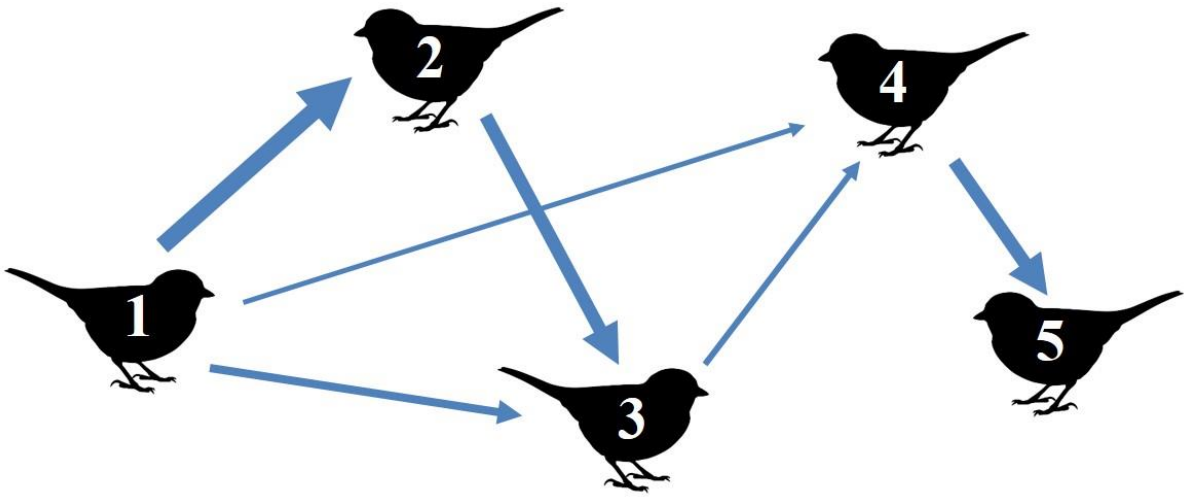

Figure 1.1 Basic social network diagram illustrating nodes (numbered bird diagrams) connected by weighted, directed edges (arrows).

Network diagrams are an informative way to portray the interactions occurring within a population, and allow inference of basic population patterns, such as structuring into distinct units, or whether there are clear dominant or central individuals in social structures (Scott 1988; Farine and Whitehead 2015). Network visualisation can also assist with development of hypotheses about the underlying causes of observed patterns of contact. However, a deeper understanding of the processes underpinning contact patterns requires the characterisation and analysis of a network's structure. For example, if a population is geographically separated into two or three disparate sub-populations, then any interaction between individuals in those sub-populations is of particular interest, as it is unlikely to be random (Weber et al. 2013; VanderWaal et al. 2016). Key individuals, structural features and processes can be identified by highlighting the properties shared by nodes, and by examining distinct networks for similarities. Node-based metrics are those which examine the distinct nodes that make up a network, and how they relate and contrast to one another (Borgatti et al. 2013). Many node-based metrics are derivatives of centrality measures, which differentiate the importance or influence of each individual in a population (Borgatti 2005). They include such measures as degree (the number of edges a node is connected to), *x*-step reach (the number of other nodes which can be reached by *x* steps), betweenness (the number of paths between node pairs that pass through a given node) and strength (the sum of edge weights connected to a node). Network-based metrics are commonly the mean, correlations or distribution of given node-based measures e.g. mean betweenness, degree distribution; these can also be compared between networks. See Table 1.1 for a glossary of common node and network-based metrics.

Metric	Level	Definition
Degree	Node	Count of the number of edges connected to a node. Can be binary or weighted by the sum of all edge weights connected to a node. Highlights well connected nodes.
Betweenness	Node	Number of shortest paths that flow through a node. Measure of how critical a node is for connecting disparate parts of a network.
Reach	Node	Measure of the proportion of all other nodes that can be reached in *x* number of steps. Measures the nodes with the highest potential to reach the entire network in the shortest number of steps.
Closeness	Node	The sum of all the shortest paths (between all other nodes) flowing through a node, this measure is indicative of how close a node is to all others within a network. Highlights the nodes that are best place to influence the entire network most quickly.
Clustering coefficient	Node	Measure of the number of a node's connections that are also connected to one another. Indicative of the tendency for clusters of closely connected individuals to form within a network.
Density	Network	The proportion of edges that exist within a network, as opposed to all those that could possibly exist with complete interconnectivity.
Assortativity	Network	A measure of how likely nodes are to position themselves in close proximity to similar nodes.
Transitivity	Network	The proportion of triads (clusters of three nodes) that are completed. Captures the level of clustering occurring in the network as a whole.

Table 1.1 Glossary of common measures used in SNA, whether they are a measure of node or network level patterns and a brief description of their utility (derived from Borgatti et al. 2009; Farine and Whitehead 2015).

Social network analysis has been used with increasing frequency in biology in recent years due to its ability to illuminate the processes underpinning population structuring and the specific behavioural influences of individuals or social groups (e.g. in mammals – Allen et al. 2013; Goldenberg et al. 2016; Fedurek et al. 2017; Silk et al. 2018; birds – Farine et al. 2012; Aplin et al. 2015; Firth et al. 2016; Boogert et al. 2018; reptiles – Godfrey et al. 2014; Riley et al. 2018; fish – Haulsee et al. 2016; Krause et al. 2016; DeOliveira et al. 2019) . One of its strengths is allowing insight into the social complexity inherent in animal societies, as well as the spread of processes that occur at the population level and how they manifest themselves at higher organisational levels (Borgatti et al. 2009). This makes it ideally suited to disease ecology, allowing investigation of how population and social structure might influence the spread of wildlife diseases (Craft 2015).

Behaviour and disease transmission through social networks

Disease transmission is driven by individual-level behaviours in many host-disease systems. Additionally, infection itself can have effects on animal behaviour which often serve to facilitate or reduce further transmission (Dizney and Dearing 2013). The nature of these factors means they have reciprocal effects, with behaviour influencing likelihood of disease transmission while infection can in turn influence behaviour of the infected animal. As a result, the effects of animal behaviour on disease transmission, and vice versa, are critical to our understanding of how disease spreads in free-living wildlife populations. Social network analysis represents one of the best ways to investigate the effects of individual behaviour on higher scale disease dynamics (Silk et al. 2017a).

Social network analysis has been utilised to better understand the dynamics of a variety of host-pathogen systems (White et al. 2017). The approach is useful in both tracking and predicting outbreaks of novel pathogens in real time, including in humans. Close studies of people's interactions with one another and how they influence transmission in the early stages of disease spread have been used to help manage outbreaks of critical diseases such as Ebola (Rizzo et al. 2016), SARS (Meyers et al. 2005) and various strains of influenza (Cauchemez et al. 2011; Davidson et al. 2015). In wildlife, a social network-based approach has been used to analyse systems as diverse as rabies outbreaks in raccoons (*Procyon lotor*; Reynolds et al. 2015; Hirsch et al. 2016) and spread of intestinal pathogens in bumble bees (*Bombus impatiens*; Otterstatter and Thomson 2007). The ability to break down populations into distinct units has also facilitated study of complex multi-species systems, including tuberculosis in badgers (*Meles meles*) and cattle (Drewe et al. 2013; Weber et al. 2013; McDonald et al. 2018) and cross-transmission of pathogens that can be spread between various bat species (Luis et al. 2015). Using SNA has allowed better understanding of disease processes in these systems, as well as accurate modelling of potential outbreaks.

Considering how individual behaviour shapes transmission dynamics is particularly importance in disease ecology, where transmission is dependent on interactions between infected and susceptible hosts. The probability of these contacts occurring is intrinsically driven by heterogeneities in contact patterns. A historical limitation of epidemiological studies has been the assumption that contacts between individuals in a population are entirely random and based around a mean rate (McCallum et al. 2001). In reality this is very seldom accurate (Woolhouse et al. 1997). Individual contact rates can fluctuate widely due to multiple factors, from seasonal variations (Blaszczyk 2017; Silk et al. 2017b) to social dominance (Bierbach et al. 2014; DeOliveira et al. 2019) to the effects of infection itself

(Dawson et al. 2018). Therefore, a small number of individuals can have a disproportionate effect on disease transmission. These individuals (known as "superspreaders") represent a small proportion of the population being responsible for a high proportion of new infections (Lloyd-Smith et al. 2005). The opposing effect may also be a factor, with some individuals proving to have a hyper-competence to infection, effectively shielding a proportion of the population from disease (Martin et al. 2019). Identifying these heterogeneities greatly improves our understanding of disease dynamics, but requires viewing populations as aggregations of autonomous individuals. Such a view shifts our focus away from making generalisations about population units, and allows more refined, individual focused parameterisation of important epidemiological parameters.

Our comprehension of how disease affects wildlife populations is largely facilitated by accurate computation of key parameters relating to the behaviour of an infection in relation to its host. These include: basic reproduction number of the infection (R_0) – the number of secondary infections produced (Diekmann et al. 1990); transmission probability (γ) – the probability of transmission given a contact between an infected individual and an uninfected individual (May and Lloyd 2001; Craft 2015); transmission rate (β) – the rate of disease transfer given the frequency of contacts between infected and susceptible individuals and the transmission probability (McCallum et al. 2017). These critical epidemiological parameters all require a form of estimate of contact rates occurring within susceptible populations. The ability to gather detailed data on contact rates in wildlife was limited in the past, resulting in the majority of epidemiological models assuming random mixing (Bansal et al. 2007). However, recent advances in technology have allowed collection of comprehensive data on contact rates over prolonged periods (Prange et al. 2006; Cross et al. 2012). These advances have facilitated the integration of SNA into epidemiological studies, vastly increasing our

capacity to understand and make realistic predictions of disease dynamics (Drewe et al. 2013; Reynolds et al. 2015; White et al. 2017).

Tasmanian devils (S*arcophilus harrisii*) and devil facial tumour disease (DFTD)

Tasmanian devils are the world's largest remaining marsupial carnivore, filling a vital role in the Tasmanian ecosystem (Rose et al. 2017). Formerly present across a wide range on the Australian mainland, they are now endemic to the island state of Tasmania (Brüniche-Olsen et al. 2014; White et al. 2018). Devils are nocturnal predators, with a variety of specialisations for scavenging, including an exceptional sense of smell and dentition well adapted to crushing and grinding bone (Jones et al. 2003; Attard et al. 2011). They are solitary, non-territorial animals with over-lapping home ranges (Guiler 1970). Aggregations often occur around food sources where agonistic behaviours are common (Pemberton and Renouf 1993; Hamede et al. 2008). Devils are sexually dimorphic, with males attaining an upper weight of 9 kg on average and females 6 kg (Rose et al. 2017). Lifespan is relatively brief for a medium-sized mammal, seldom exceeding 6 years in the wild (Guiler 1978). Animals reach sexual maturity at 2 years of age (Rose et al. 2017), though a fraction of females breed as yearlings (Jones et al. 2008). The majority of breeding occurs over a two-month period from mid-February until mid-April, when most females enter oestrous (Hesterman et al. 2008). Mating interactions can be aggressive, with males actively retaining females within a den for a period of days (Buchmann and Guiler 1977). Agonistic interactions between devils, both at feeding sites and during mating interactions, can result in bite wounds – the primary form of transmission for their transmissible cancer, DFTD (Hamede et al. 2013).

DFTD emerged in north-eastern Tasmania in 1996 and has since spread to cover almost the entire distributional range of the devil (Hawkins et al. 2006; Woods et al. 2018). DFTD is a directly transmissible cancer, of Schwann cell origin (Murchison et al. 2010), in which the tumour cells themselves are the infectious agent. Transmission between individuals occurs via allograft (Pearse and Swift 2006), with the immune system of the new host failing to recognise the foreign cells due to downregulation of MHC molecules by the tumour itself (Siddle et al. 2013). Bite wounds represent the pathway through which tumour cells transfer between individuals (Hamede et al. 2013), with the majority of primary tumours presenting around the face and oral cavity of the host. The disease is almost invariably fatal, though rare instances of recovery have been documented (Pye et al. 2016a; Margres et al. 2018b).

As DFTD has progressed, increasing efforts have been made to understand its origins and effects in devil populations, as well as the adaptive processes that are occurring in both devils and tumours (Woods et al. 2018). The effects of the disease can vary on a local scale, with some populations proving more resilient than others (Hamede et al. 2012), while the emergence of different lineages of tumour has resulted in divergent infection rates and host responses (Hamede et al. 2015). On a wider scale, devil life history has altered rapidly in response to disease pressure (Jones et al. 2008; Russell et al. 2018), while alterations in the devil genome have occurred in a relatively short number of generations (Epstein et al. 2016; Margres et al. 2018a). More recently, a second transmissible cancer, DFT2, has been identified in southern Tasmania (Pye et al. 2016b), with mutation patterns indicating the two tumour lines arose independently, but by similar mechanisms (Stammnitz et al. 2018). The emergence of the second transmissible cancer in devils indicates that the species may have an inherent vulnerability to this form of cancer. This vulnerability may be enhanced by the nature of devil's interactions with one another providing a clear pathway for transmission.

The behaviour of devils plays a major role in the transmission of DFTD, with transfer of tumour cells requiring animals to physically bite one another. The tendency to bite or be bitten varies between individual devils (Hamede et al. 2013), meaning that 1) the high mortality rate of DFTD will exert selective pressure on behavioural traits that confer a reduced likelihood of infection and 2) the role of individual devils in driving transmission dynamics would be expected to vary. Additionally, it has previously been shown that devil contact networks are both highly connected and seasonally variable (Hamede et al. 2009), so likely to play a key role in disease dynamics. However, devil interactions and network position have never been investigated in tandem with biting behaviour – the critical transmission point for DFTD.

Thesis aims and outline

In this thesis I investigate the role of behaviour and social networks in the dynamics of DFTD infection. The studies presented here represent a progression from investigating patterns in devil behaviour, interactions and social network properties to how they influence transmission of DFTD through a devil population in real-time.

In Chapter 2, I examine the variation in individual behaviour of Tasmanian devils. I investigate the relative flexibility of devil behaviour in response to a novel stimulus, and whether behavioural patterns exist in relation to individual traits and aspects of disease history.

In Chapter 3, I monitor all close-range interactions occurring within a disease-free Tasmanian devil population over a six-month period using proximity-loggers. I use these data to create seasonal contact networks and details of behavioural patterns and investigate how these relate to number of bite wounds animals accrue (effectively a proxy of DFTD-infection risk).

In Chapter 4, I use the interaction and bite wound data collected from the disease-free population to parameterise network models predicting the spread of DFTD through this susceptible population over a ten-year period. Networks are created using 1) all close-range interaction data, and 2) purely data on bite wounds accrued, in order to examine the divergences in predictions of key epidemiological parameters (β and R_0) produced by modelling on contact or transmission-based networks.

In Chapter 5, I closely monitor the early stages of DFTD spread through a susceptible Tasmanian devil population using regular captures and proximity-logging technology. With this study I present the first detailed data on how DFTD spreads in the early stages of infection. I use these data to investigate whether the behaviour of devils alters upon DFTD infection and progression, and whether position within a social network heightens devil's vulnerability to infection in the short-term.

Finally, in Chapter 6, I synthesise all results, before discussing their applications to both Tasmanian devil management and disease ecology more generally. I finish by identifying current research gaps and possible future directions.

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Chapter 2

Behavioural response to the threat of DFTD in Tasmanian devils

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ABSTRACT

Animal behaviour is important in the disease transmission process. Infection risk can inflate or reduce as a function of the way an animal behaves. In the case of the Tasmanian devil (*Sarcophilus harrisii*) and its transmissible cancer, devil facial tumour disease (DFTD), behaviour plays a key role, as the disease is transmitted via biting. We examined the response of devils from sites across Tasmania (with varying times since first infection with DFTD) to a novel stimulus – capture and handling – to assess whether devil behaviour is related to bite wounds, the sites of transmission, and whether behaviours change with exposure to DFTD on a rapid evolutionary time-scale. Devils displayed a degree of flexibility in their response to handling, though this varied at the individual level. Reactivity of devils was found to relate strongly to sex, season, DFTD status, number of years since site infection with DFTD and the number of wounds the animal was carrying. The results indicate that reactive devils are more prone to picking up high numbers of bite wounds, potentially inflating their chance of DFTD infection. A reduction in reactivity at sites which have carried DFTD for greater periods suggests a selective pressure against reactivity and particular behaviour types driven by the threat of DFTD infection.

INTRODUCTION

Behaviour plays a key role in the transmission of parasites and pathogens. The way a host interacts with its environment and conspecifics can alter its likelihood of being involved in a transmission event. Host behaviour can be self-adjusted to reduce or avoid infection, be manipulated by parasites and pathogens to increase the probability of infection and can change as a result of infection itself (Dizney and Dearing 2013; Ezenwa et al. 2016). If behaviours are heritable, selection could result in behavioural shifts in a population if particular behavioural types are more susceptible to infection. Behavioural changes are driven by attributes of the host-pathogen system, such as pathogen life cycles, mode of transmission and virulence levels (Hart 1990; Curtis 2014; Vittecoq et al. 2015). Thus, there is an interaction whereby behaviour alters disease spread, but that disease transmission dynamics can also alter behaviour.

The mechanisms through which behaviour can influence pathogen spread are highly dependent on the transmission pathway of the particular pathogen. Pathogens which are transferred between individuals via direct inoculation in bodily fluids, such as rabies and many sexually-transmitted diseases, can directly benefit from increased close contact between hosts (Hampson et al. 2009; Flint et al. 2016). Transmission can be increased by a variety of behaviours, such as heightened aggressive tendencies (Klein 2003; Zohdy et al. 2017) or an alteration to movement patterns (Altizer et al. 2011; Satterfield et al. 2015). For hosts, the likelihood of becoming infected can be drastically reduced by avoiding contact with infected individuals (Curtis 2014; Vilches et al. 2019), or through avoidance of behaviours likely to result in opportunities for transmission (Weinstein et al. 2018). From the perspective of the pathogen or parasite, behavioural manipulation of host behaviour can allow

increased opportunities for further transmission. For example, parasites which require specific criteria to complete their life cycle can manipulate the behaviour of host individuals to promote social isolation or the seeking out of abnormal conditions (Thomas et al. 2010; Andriolli et al. 2019). While the nature of the host-parasite system influences the types of behaviour that are adaptive, the strength of selection pressure (driven by fitness costs such as morbidity and mortality rates) will influence how rapidly a behavioural trait with an inherited component becomes widespread in a population.

Heritable behavioural traits that are under strong selection can result in rapid phenotypic change over a small number of generations. From a host perspective, behaviours that result in a reduced probability of infection should be selected for when infection reduces fitness, since they increase the host's odds of surviving and reproducing (Kiesecker et al. 1999; Curtis 2014). As infections become endemic, shifts in behavioural phenotype of such heritable behaviours should become apparent within and between populations with time since a disease outbreak. The potential for these effects is apparent in systems such as outbreaks of chytridiomycosis in amphibian populations. Infection with chytrid reduces markedly in individuals which spend increasing amounts of time above the pathogen's upper optimum temperature (Woodhams et al. 2003). Mean body temperature has been shown to increase in populations of frogs after the first appearance of the pathogen (Richards-Zawacki 2010), linked to alterations in their thermal behaviour (Rowley and Alford 2013). Rapid heritable behavioural responses to infective agents have also been observed in species with short generation times, such as bees. For example, multiple populations of Western honey bees (*Apis mellifera*) avoid infection by the ectoparasitic mite *Varroa destructor* as a direct result of a rapid, plastic behavioural shift, in which they increase vigilance and destructive targeting of mite-infested cells much more effectively than local susceptible colonies (Oddie et al.

2018). Rapid behavioural alterations in response to disease outbreak can not only assist the survival of individual hosts in the short term, but also the persistence and adaptability of populations over time.

Changes in host behaviour due to disease emergence should be expected in cases where infection incurs a high fitness cost (Ujvari et al. 2016). Potential behavioural shifts associated with a reduced likelihood of infection can be evaluated on a temporal spectrum, from disease-free to diseased populations and across generations. Shifts in prevalence of different behaviour types with increasing time since disease provides a good indicator of the selective forces that may be at work in the population. The Tasmanian devil (*Sarcophilus harrisii*) and its novel transmissible cancer, devil facial tumour disease (DFTD), provides an opportunity to investigate the effects such a strong selective force can exert on behaviour patterns within populations over time.

Tasmanian devils have been under threat from DFTD for over 20 years (Hawkins et al. 2006), with in excess of 90% local population declines (Lachish et al. 2007) as the disease spreads across their geographic range in Tasmania (Lazenby et al. 2018). The disease is transmitted when susceptible and infected devils bite one another. The requirement of close contact and open wounds for tumour cells to infect a susceptible animal means that aggressive behaviour plays a critical role in DFTD transmission. However, devils with fewer bite wounds are at higher risk of developing DFTD, suggesting that it is the aggressive animals that inflict bite wounds on others, rather than individuals receiving bite wounds, that are at a higher risk of becoming infected (Hamede et al. 2013). With close to 100% mortality from DFTD once an individual becomes infected, such a high fitness cost should result in

strong selection pressure favouring the survival and fitness of less aggressive individuals. Devils respond remarkably rapidly to the extreme mortality caused by DFTD, both in phenotypic plasticity and rapid evolution. Devil populations have undergone rapid life history shifts in just a few years following local disease outbreak and host population decline (Jones et al. 2008). Up to 50% of females are able to reach a critical body mass to breed precocially in their first year of independent life; a consequence of higher growth rates in juveniles with reduced competition for resources as populations fall below carrying capacity (Lachish et al. 2009). While life history changes may be evidence of plasticity, devils have shown rapid evolution in regions of the genome associated with fighting cancers and immune response (Epstein et al. 2016). This rapid evolutionary response has occurred in as little as 4-6 generations following local disease outbreak, suggesting that selection is operating on standard genetic variation present prior to DFTD emergence and that devils have plenty of adaptive potential. Given that DFTD is a cancer with extremely high mortality and Tasmanian devils have a relatively short generation time (two years) a reduction in behaviours associated with likelihood of becoming infected is expected as the epidemic unfolds. Devils are cryptic, and difficult to observe directly in the wild across a range of situations, however, inferences about their behaviour can be made based on how they respond (i.e. their reactivity, or responsiveness, level) to a novel situation, such as being caught and handled by humans. Their flexibility in altering this reaction behaviour with increasing habituation may also give an indication of how rapidly they are able to alter their behaviour in response to a new threat.

We analyse a large dataset in which a suite of behaviours displayed by individual devils when they were caught and handled for DFTD monitoring surveys were recorded. The data were collected between 2015 and 2018 at five sites where DFTD has been present for differing

periods of time, as well as a disease-free population. We ask the following questions - 1) Is devil behaviour upon capture repeatable through time, or flexible in response to increasing familiarity? 2) Are there differences in behavioural responses in populations with varying periods since DFTD arrival, as well as differences amongst sexes, times of year, DFTD status or the numbers of wounds being carried by an animal? A reduction in a behaviour with increasing time since DFTD infection would indicate that it is being selected against. Further, the number of wounds being carried is a particularly important variable to investigate, as wounds represent opportunities for disease transmission and have been shown to influence the likelihood of acquiring DFTD previously (Hamede et al. 2013).

MATERIALS AND METHODS

Study sites and data collection

The study was conducted on six populations of Tasmanian devils situated across Tasmania (Figure 2.1). One of these populations (Arthur River) was disease-free at the time of sampling and the remaining five had been infected with DFTD for different time-frames at the onset of the study, from 14 years (Freycinet National Park) to 1 year (Black River); see Table 2.1 and Figure 2.1. All devils were caught between 2015 and 2018 in DFTD-monitoring surveys across the state. The animals were caught using PVC pipe traps, baited with meat (macropod, lamb) overnight and checked from first light every morning. Generally, 40 traps were deployed for 10 nights at each site, over an area of around 25 km^2.

Site	Number of years since DFTD arrival	Number of Individuals	Number of Captures
Arthur River	-	172	282
Black River	1	160	361
Takone	5	198	529
Wilmot	7	135	232
West Pencil Pine	9	150	403
Freycinet	14	154	303
Total		969	2110

Table 2.1 The number of years (as of commencement of data collection in 2015) since the first record of DFTD at each site, and the number of individuals and captures recorded from 2015 to 2018.

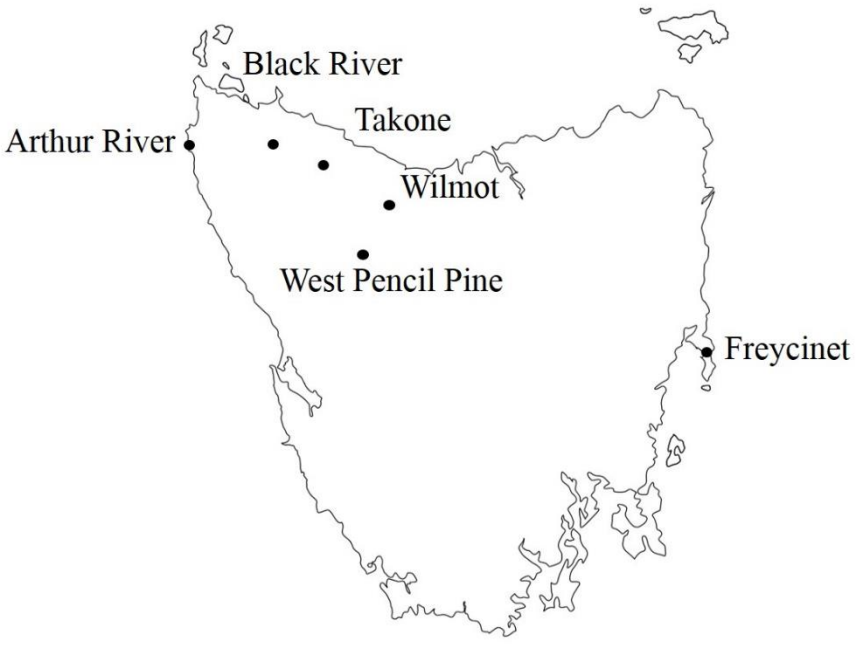

Figure 2.1 Name and location of sites from which devils were sampled across Tasmania.

Upon capture, each animal underwent a standardised measurement and sample collection procedure, including morphometrics, blood sampling, hair and whisker sampling, and tissue and tumour biopsies. These were done by placing the animal in a hessian sack, and gently moving it into different positions on the handler's lap, so different parts of the body could be accessed. On the first capture only, all individuals were permanently marked with a subcutaneous microchip (AllFlex© ISO FDX-B) and had a small tissue biopsy taken from the base of their right ear for genetic research. During the handling procedure, animals were checked all over the body for fresh bite wounds and tumours (see Hamilton et al. 2019 for further details). The animal's eyes remained covered throughout the procedure. The entire process generally took no more than 30 minutes, after which the animal was released at the point of capture. Animals caught on multiple instances on the same 10-day trip were released without handling from the second instance onwards. Time intervals between trapping trips were generally three months, with animals handled, measured and sampled again during their first capture on each subsequent trip.

During the handling procedure, a suite of behaviours displayed by the animal were recorded. These behaviours have been categorised for quantifying behavioural variations in wild and captive Tasmanian devils previously (Pemberton and Renouf 1993; Jones and Sinn, unpublished). All behaviours and their descriptions are included in Table 2.2. All behaviours were given a score between 0 and 2, where 0 indicates the behaviour was not displayed, 1 that the behaviour was displayed once, and 2 that the behaviour was displayed multiple times.

Behaviour	Description
Trembling/Jumpy	Shaking or quivering / responds to being touched by pulling away
Urination/Defecation	Urinates or defecates while being handled
Farting	Breaks wind
Mouth Gaping	Opens, and holds open, mouth without handler intervention
Biting (&/or attempt)	Either bites or makes clear attempt to bite the handler
Huffing	Deliberate sharp exhalation of air
Jaw Clomping/Lip Smacking	Hard closure of jaws making a clear, wet, sound and moves tongue against jaws and lips
Growling	Snarling, spitting noise made
Screeching	Escalation of vocalisation to high pitched screeching noise
Struggling	Clearly pushes back against handler whilst being positioned for measurements/samples

Table 2.2 Behaviours and a short description of their context and identification.

Data handling and statistical analysis

Behavioural categories

Prior to conducting analysis, we ran Pearson's correlation tests between all pairs of behaviours and a Principal Components Analysis (PCA) of all behaviours together. Three pairs of behaviours were both highly correlated (Pearson's correlation) and paired in the PCA (see Supplementary Materials 2.1), so were each combined into single variables. These pairs were - mouth gaping and biting ($r = 0.74$); huffing and jaw clomping ($r = 0.58$); growling and screeching ($r = 0.81$). The pairings of each set of behaviours make biological sense, as they are all escalations of a form of display behaviour. Mouth gaping is a behaviour performed by

devils as a precursor to attempting to physically bite; huffing is one of the most common vocalisations made, with the next stage in a threat display being to clomp their jaws; growling is a vocalisation that can escalate in a graded sequence which culminates with screeching (Pemberton and Renouf 1993).

Inter-observer bias

To test for observer bias in scoring behaviours (as the data was collected by 4 different handlers; DH, RH, MR and SC), a subset of individuals (n = 36) were processed by 2 handlers at the same capture event. Each handler independently (and blindly) submitted a behavioural score for the individual, with the order in which the animal was processed by each handler alternated. To test for any effect of handler on each of the behaviours measured, we ran a series of generalised linear mixed models (GLMMs) in the R package *lme4* in R 3.5.2 (R Core Team 2018*)* with a behavioural type included as the response variable in each, and individual and handling order as random factors. Handler was not found to have a significant effect on the value of any of the behaviours measured ($p = 0.52 – 1.00$). Of the 36 individuals scored, scores given by each handler were identical in 31 instances. The 5 instances in which this was not the case, the score was different by a maximum of 1 and never the result of a particular behaviour having been interpreted differently. The low observer bias is probably due to the behaviours being quite unambiguous to score. None of the behaviour scores recorded for the inter-observer bias tests were used in the final analysis.

Repeatability of behaviours within individuals

We tested the repeatability of the number of different behaviours exhibited by an individual devil during a handling event, as well as each of the individual behaviours, across captures

using the R package *rptR* (Nakagawa and Schielzeth 2010). Individual behaviours were treated as a binary variable for this analysis, with a 1 being scored if a behaviour was performed at any frequency, and a 0 being recorded if it was not displayed. Only individuals that were caught and handled twice or more were included in this analysis. We estimated LMM-based repeatability of the overall number of behaviours displayed between capture events, in addition to that of each of the seven behaviour types individually. As devil behaviour is likely to alter seasonally, we included season (mating or non-mating season) and whether the animal was carrying pouch young as fixed effects. 'Number of behaviours' was treated as a variable with a Poisson distribution, as the data were skewed toward low numbers of different behaviours. All individual behaviours were modelled as binary variables (exhibited behaviour or not). For each repeatability estimate, non-parametric bootstrapping was applied to calculate 95% confidence intervals based on 1000 bootstrapping runs and 1000 permutations. All statistical analyses were performed using R 3.5.2 (R Core Team 2018).

Predictors of behaviours displayed

We tested the effects of four factors on the number of behaviours displayed by individuals on capture: *sex* – male or female; *season* – whether the capture was in the Tasmanian devil mating season (15th February to 15th April; see Hamilton et al. 2019) or not; *DFTD status* – whether the animal displayed clinical signs of DFTD or not; *years since disease* – the number of years between DFTD first being recorded in the sampled population and the first sampling effort used in this analysis; *bite wounds* – number of fresh bite wounds recorded on an animal during handling. To analyse the effects of these factors on the response variable, the number of behaviours displayed, we fitted ordinal mixed models (OMMs) using the R package

ordinal (Christensen 2018). OMMs were used to account for the fact that steps between behaviour numbers are non-linear, but do represent an increasing level of reactivity to handling (Patrick et al. 2013; Harrell 2015). Individual/capture number was fitted as a random factor to account for any propensity for animals' behaviour to change predictably with increasing number of captures. We used a multi-model inference approach to rank models (Burnham and Anderson 2002) and Akaike's Information Criterion corrected for small sample size (AICc; Hurvich and Tsai 1989), in the *AICcmodavg* package. To investigate whether any patterns found were being driven by a particular behaviour type, we also fitted OMMs with the score for each individual behaviour as the response variable, ranking each set using AICc.

RESULTS

Repeatability of behaviours within individuals

Within-individual repeatability of the number of behaviours displayed on capture was moderate (*R*: 0.52 [CI: 0.41-0.55]; Table 2.3) and strongly influenced by the presence of pouch young in females ($P = 0.001$). At the level of separate behaviour types, trembling/jumpy (*R*: 0.41 [CI: 0.25-0.47]; Table 2.3), huffing/jaw clomping (*R*: 0.59 [CI: 0.12-0.76]; Table 2.3) and struggling (*R*: 0.39 [CI: 0.24-0.45]; Table 2.3) behaviours were moderately repeatable at the individual level. Trembling/jumpy behaviour was more likely to be observed in the non-mating season ($P = < 0.0001$), while struggling behaviour was more likely to be observed in females carrying pouch young ($P = < 0.01$). None of the other behaviours investigated had repeatability scores in excess of 0.3, nor did they show any influence of season or as a result of carrying pouch young (Table 2.3).

Parameter	Repeatability (*R*)	S.E.	Seasonal influence	Influence of PY
Number of behaviours	0.52	± 0.04	0.05	0.001*
Trembling/Jumpy	0.41	± 0.06	< 0.0001*	0.74
Urination/Defecation	0.04	± 0.002	0.20	0.50
Farting	0.24	± 0.06	0.86	0.15
Mouth Gaping/Biting	0.13	± 0.002	0.45	0.84
Huffing/Jaw Clomping	0.59	± 0.17	0.29	0.16
Growling/Screeching	0.14	± 0.003	0.8	0.73
Struggling	0.39	± 0.06	0.04*	< 0.01*

Table 2.3 Repeatability estimates for the number of different behaviours displayed and for each individual behavioural type for wild Tasmanian devils. P-values of the fixed effects in each model (season and presence of pouch young) are also included.

Predictors of behaviours displayed

The single top ordinal model assessing the number of behaviours displayed by Tasmanian devils on capture retained all variables (Table 2.4). The next ranked model was only separated by ΔAICc of 1.37 (Table 2.4) and included all variables except DFTD status. After this, the next model was separated by a large margin of 14.64 ΔAICc. In the best supported models, sex, season, years since DFTD and number of wounds had strong influence on the number of behaviours displayed. Males were predicted to display 0.44 more behaviours than females, while 0.38 fewer behaviours were predicted in devils caught during the mating season (Table 2.4). There was a reduction in number of behaviours displayed of 0.05 per year that DFTD had been present at the site at which a devil was caught. Number of behaviours an animal displayed was predicted to increase by 0.11 for every wound it was carrying.

K	AICc	ΔAICc	AICc Wt	Cum. Wt	Sex (M)	Season (Mating)	DFTD (+)	Years since DFTD	Nº Wounds
12	5136.38	0	0.66	0.66	0.44 ±0.12	- 0.38 ±0.14	0.25 ±0.13	- 0.05 ±0.002	0.11 ±0.002
11	5137.75	1.37	0.33	1.00	0.43 ±0.14	- 0.38 ±0.14	-	- 0.05 ±0.015	0.11 ±0.019
9	5151.02	14.64	0.00	1.00	-	-	-	- 0.05 ±0.015	0.11 ±0.018
Relative importance of variable					**1.00**	**1.00**	**0.66**	**1.00**	**1.00**

Table 2.4 Parameter estimates for ordinal mixed models assessing biological and disease-related patterns of variation in the number of behaviours displayed by devils on capture. Models were ranked according to Akaike's Information Criterion corrected for small sample sizes (AICc); values for difference in AICc (ΔAICc) from the previous model, model weight (AICc Wt) and cumulative model weights (Cum. Wt) are displayed, along with the relative importance of each variable across the entire model set. Only the top three models are listed, unless a higher number than this failed to exceed a threshold of ΔAICc < 5. Individual identity was included as a random effect in each model.

When the separate behaviours were examined independently in seven series of ordinal mixed models, similar predictions were made for three behaviour types – trembling/jumpy, mouth gaping/biting and struggling. Predictions for the remaining four behaviour types (urination/defecation, farting, huffing/jaw clomping and growling/screeching) were found not to differ significantly (> 5 ΔAICc) from the null model (see Supplementary Materials 2.2 for AICc tables).

The ordinal model best explaining patterns in trembling/jumpy behaviour retained all variables (sex, season, DFTD status, years since DFTD arrival and number of wounds), though differed from the next best model (dropping only DFTD status) by only 0.25 ΔAICc; the next ranked model (retaining only years since DFTD and number of wounds) differed by a large margin of 18.68 ΔAICc (Table 2.5a). In the top-ranked model predicting trembling/jumpy behaviour, males displayed the behaviour more, as did DFTD positive animals and those carrying high numbers of bite wounds. The same model indicated a negative effect of season (mating) and number of years since DFTD arrival (Table 2.5a). Of the ordinal models predicting mouth gaping/biting behaviour, the top model retained all variables and differed from the next best model (retaining wounds only) by 3.04 ΔAICc (Table 2.5b). Effect patterns were consistent with the trembling/jumpy model results, though the negative effect of mating season and number of years since DFTD was lessened, while positive effect of DFTD status was heightened (Table 2.5b). The top model predicting struggling behaviour retained all variables and was strongly supported, differing from the next best model (dropping only DFTD) by 11.43 ΔAICc (Table 2.5c). Males were observed to struggle more, as were animals displaying clinical symptoms of DFTD and those carrying high numbers of wounds. Animals struggled less in the mating season, and there was a reduction in struggling behaviour with increased time since DFTD arrival (Table 2.5c).

2.5a) Trembling/Jumpy

K	AICc	ΔAICc	AICc Wt	Cum. Wt	Sex (M)	Season (Mating)	DFTD (+)	Years since DFTD	Nº Wounds
8	2471.38	0	0.53	0.53	0.33 ±0.17	- 0.86 ±0.21	0.26 ±0.17	- 0.04 ±0.02	0.15 ±0.02
7	2471.64	0.25	0.47	1.00	0.32 ±0.17	- 0.87 ±0.21	-	- 0.04 ±0.02	0.15 ±0.02
5	2490.06	18.68	0.00	1.00	-	-	-	- 0.03 ±0.02	0.15 ±0.02
Relative importance of variable					**1.00**	**1.00**	**0.53**	**1.00**	**1.00**

2.5b) Mouth Gaping/Biting

K	AICc	ΔAICc	AICc Wt	Cum. Wt	Sex (M)	Season (Mating)	DFTD (+)	Years since DFTD	Nº Wounds
10	1301.64	0	0.68	0.68	0.46 ±0.48	- 0.14 ±0.37	1.01 ±0.38	- 0.002 ±0.06	0.13 ±0.04
6	1304.68	3.04	0.15	0.83	-	-	-	-	0.12 ±0.04
6	1305.65	4.00	0.09	0.92	-	-	0.91 ±0.31	-	-
Relative importance of variable					**0.68**	**0.68**	**0.77**	**0.68**	**0.83**

2.5c) Struggling

K	AICc	ΔAICc	AICc Wt	Cum. Wt	Sex (M)	Season (Mating)	DFTD (+)	Years since DFTD	Nº Wounds
8	2611.67	0	1.00	1.00	0.37 ±0.16	- 0.49 ±0.004	0.61 ±0.16	- 0.04 ±0.02	0.12 ±0.004
7	2623.10	11.43	0.00	1.00	0.36 ±0.48	- 0.51 ±0.19	-	- 0.04 ±0.02	0.12 ±0.02
5	2630.74	19.08	0.00	1.00	-	-	-	- 0.03 ±0.02	0.12 ±0.02
Relative importance of variable					**1.00**	**1.00**	**1.00**	**1.00**	**1.00**

Table 2.5 Parameter estimates for the preferred ordinal mixed models assessing biological and disease-related patterns of variation in trembling/jumpy, mouth gaping/biting and struggling behaviours in Tasmanian devils. Models were ranked according to Akaike's Information Criterion corrected for small sample sizes (AICc); values for difference in AICc (ΔAICc) from the previous model, model weight (AICc Wt) and cumulative model weights (Cum. Wt) are displayed, along with the relative importance of each variable across the entire model set. Only the top three models are listed, unless a higher number than this failed to exceed a threshold of ΔAICc < 5. Individual identity was included as a random effect in each model.

DISCUSSION

Behavioural alteration is key to a host's ability to respond rapidly to novel threats and environmental disturbance. Here we have shown that Tasmanian devils are relatively flexible in their overall response to an initially novel stimulus over time but retain a lower degree of flexibility in the display of specific behaviour types (trembling/jumpy, huffing/jaw clomping and struggling). At the population level, reactivity of males was higher than females, while reactivity reduced significantly during the mating season and with increasing years since first DFTD infection. Devils carrying more bite wounds and those infected with DFTD were more reactive. Similar patterns could also be linked to three individual behaviour types – trembling/jumpy, mouth gaping/biting and struggling. Together these results indicate that devil behavioural responses are relatively flexible, but that a tendency towards reactivity may be selected against in the long-term. Reactive behaviour is likely to be associated with heightened DFTD infection risk. The action of selection against reactive behaviour is indicated by an overall pattern towards reduced reactivity in devil populations with increasing time since DFTD arrival.

The finding that repeatability was not high for either number of behaviours displayed upon capture, or for any particular response individually, indicates that at least a proportion of Tasmanian devils have a certain degree of flexibility in their behavioural responses. In some cases that flexibility may be linked to additional factors, including the presence of pouch young in females or hormonally induced seasonal changes in behaviour. There was no indication that behaviour altered predictably with increasing familiarity to capture events; some individuals retained a consistent reaction to capture through time, while others presented altered responsiveness on each capture. This indicates that, on the individual level,

Tasmanian devils vary in their tendency to mount a flexible behavioural response towards a novel stimulus. Displays of flexible behavioural responses have been associated with successful adaptation to novel conditions in other systems (Sol et al. 2002; Sih et al. 2011). Behavioural flexibility could come into play in the early stages of a DFTD outbreak, with devils that are better able to alter their response towards infected animals potentially reducing their likelihood of being involved in disease-transmitting interactions. Whether any tendency towards flexibility extends to variable behaviour in reaction to devils infected with DFTD requires further study.

Behavioural response to handling displayed a variety of patterns, with regard to both biological and disease-related factors. Males were more responsive overall, displaying a higher number of behaviours on capture. Given that responsiveness was also positively associated with high numbers of wounds, this aligns with research finding males are more likely to pick up bite wounds than females (Hamilton et al. 2019). The interaction of tendency to pick up high numbers of bite wounds with heightened responsiveness levels also makes sense in light of two further patterns – that of an increased responsiveness in devils with DFTD, and a reduction in responsiveness with increasing years since DFTD arrival at the site of capture. High numbers of bite wounds can be viewed as a corollary of infection risk, as they are the primary means of DFTD transmission to a new host (Hamede et al. 2013). Therefore, we might expect devils with high numbers of bite wounds to be more prone to DFTD infection; a pattern which we observe in the fact that responsive devils are more likely to be carrying DFTD. If responsive devils have a heightened chance of acquiring high numbers of wounds, and thus DFTD, then a reduction in the proportion of reactive devils would be expected in populations which have been infected with DFTD for a number of years – a pattern we also observe here. From the patterns observed in this study, we have an

indication that devil behaviour may be altering in response to DFTD at the population level, with a tendency towards responsiveness being selected against.

Patterns related to the number of behaviours displayed on capture were replicated for three behaviour types – trembling/jumpy, mouth gaping/biting and struggling. This would indicate that particular behaviours may be selected against, if they increase a host's likelihood of acquiring DFTD. While we cannot infer what display of these behaviours may translate to in a wild context, we are able to link tendency to display them upon capture with high numbers of bite wounds and positive DFTD status. Both of these factors suggest a net benefit (in terms of reduced disease prevalence) to an infected devil population of a reduction in occurrence of these behaviours over time.

A critical link to be made in the examination of behaviour and DFTD infection involves assessment of how behaviours exhibited by devils on handling relate to those displayed in the wild; these are the behaviours directly influencing an animal's disease susceptibility. If, for example, devils which tend to mouth gape or bite when handled are also those observed to bite conspecifics at high frequency in the wild, then we can make more inferences about what this behaviour might mean in terms of disease susceptibility. At the moment, we are able to link this behaviour, in addition to trembling/jumpy and struggling behaviour, to high numbers of bite wounds at the individual level. It has been previously quantified that devils carrying low numbers of bite wounds were those most at risk of acquiring DFTD (Hamede et al. 2013); a finding that appears contradictory to our observation of the link between high numbers of bite wounds, reactivity levels and DFTD status. The key to definitively

establishing exactly what handling behaviours represent lies in establishing if they are in any way representative of wild behaviours, and how this links to the risk of acquiring DFTD.

Transmission of DFTD in the wild is intrinsically driven by the behaviour of its host, the Tasmanian devil. The fact that the disease is transmitted between individuals via bite wounds indicates that the manner in which individual devils approach interactions with conspecifics is highly likely to affect their likelihood of acquiring the disease. Understanding infection risk at the individual level requires a detailed picture of which behaviours are likely to be directly facilitating disease transmission, and how prevalence of these behaviours may be changing over time as a result of selection. Full comprehension of behavioural mediations on infection likelihood will facilitate better informed management of devil populations, particularly by highlighting which traits are likely to be beneficial to retain in captive bred and potential release populations.

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SUPPLEMENTARY MATERIALS – CHAPTER 2

Supplementary Materials 2.1 *Principal Components Analysis*

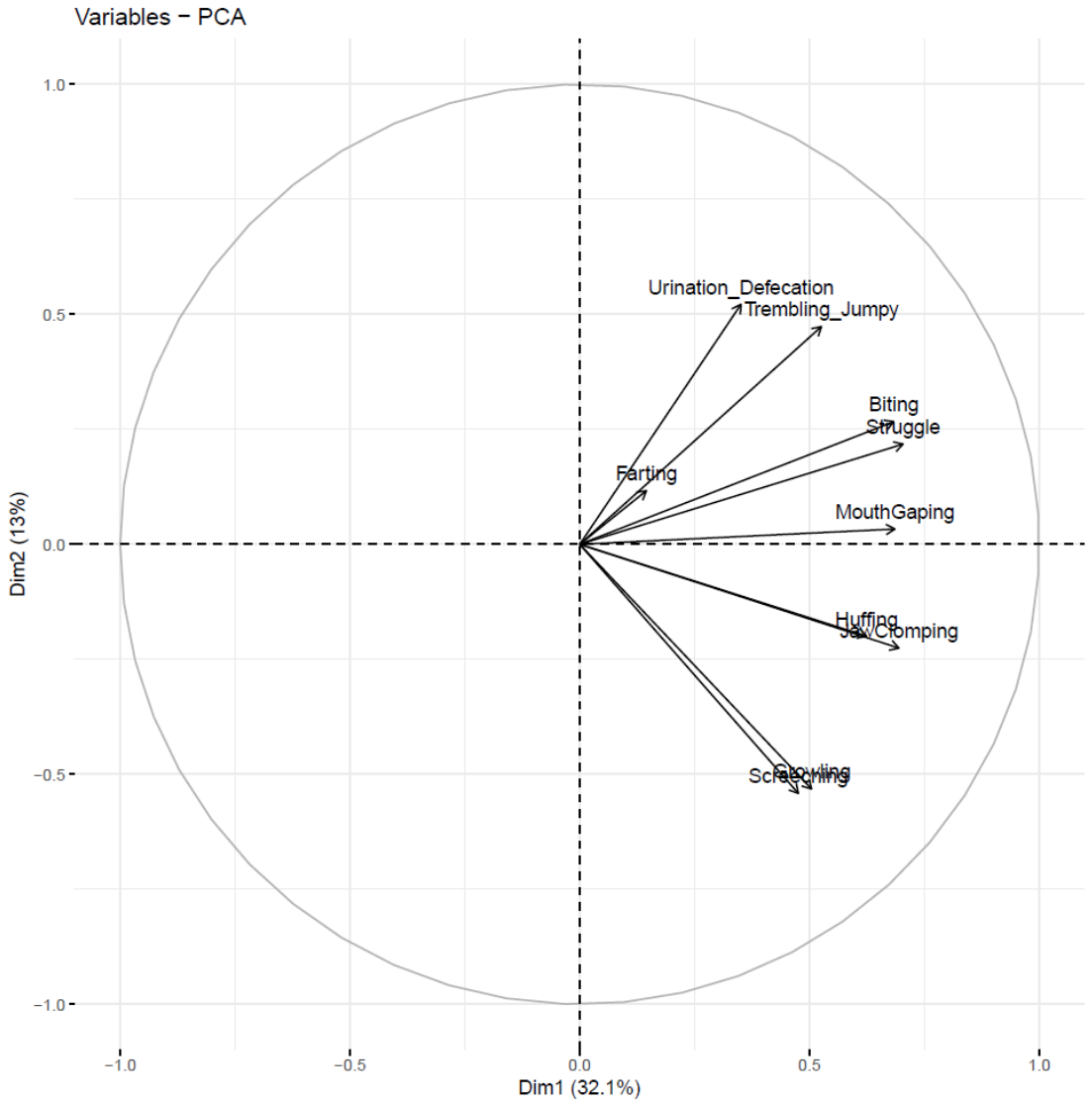

Figure S2.1 Principal components analysis of all behaviours displayed by Tasmanian devils during handling. The first two axes explain 45.1% of the variance, and group three pairs of associated behaviours that are also observed to correlate with one another; huffing/jaw clomping, growling/screeching and biting/mouth gaping.

Supplementary Materials 2.2 *Ordinal Mixed Model results for additional behaviours*

S2.2a) Urination/Defecation

K	AICc	ΔAICc	AICc Wt	Cum. Wt	Sex (M)	Season (Mating)	DFTD (+)	Years since DFTD	Nº Wounds
4	495.45	0.00	0.49	0.49	-	-	-	-	0.15 ±0.004
5	497.34	1.89	0.19	0.68	-	-	-	0.03 ±0.08	0.15 ±0.05
8	498.76	3.31	0.09	0.77	- 0.39 ±0.66	- 0.73 ±0.81	- 1.12 ±0.64	0.03 ±0.07	0.15 ±0.06
4	498.80	3.35	0.09	0.86	-	-	- 1.23 ±0.64	-	-
7	500.27	4.82	0.04	0.91	- 0.40 ±0.66	- 0.63 ±0.79	-	0.02 ±0.08	0.15 ±0.06
3	501.11	5.66	0.03	0.94	-	-	-	-	-
Relative importance of variable					**0.13**	**0.13**	**0.18**	**0.32**	**0.81**

S2.2b) Farting

K	AICc	ΔAICc	AICc Wt	Cum. Wt	Sex (M)	Season (Mating)	DFTD (+)	Years since DFTD	Nº Wounds
4	2375.24	0.00	0.23	0.23	0.33 ±0.15	-	-	-	-
4	2375.56	0.32	0.20	0.43	-	-	-	-	0.05 ±0.02
7	2376.81	1.57	0.10	0.53	0.30 ±0.15	0.03 ±0.17	-	- 0.01 ±0.02	0.04 ±0.02
5	2376.90	1.66	0.10	0.63	0.33 ±0.15	-	-	- 0.01 ±0.02	-
5	2377.05	1.81	0.09	0.72	-	-	-	- 0.01 ±0.02	0.05 ±0.02
5	2377.21	1.98	0.09	0.81	0.33 ±0.15	0.03 ±0.17	-	-	-
3	2378.37	3.13	0.05	0.86	-	-	-	-	-
Relative importance of variable					**0.52**	**0.19**	**0.00**	**0.29**	**0.39**

S2.2c) Huffing/Jaw Clomping

K	AICc	ΔAICc	AICc Wt	Cum. Wt	Sex (M)	Season (Mating)	DFTD (+)	Years since DFTD	Nº Wounds
5	1730.51	0.00	0.25	0.25	-	-	-	-	-
6	1731.83	1.32	0.13	0.37	-	- 0.24 ±0.30	-	-	-
6	1732.03	1.52	0.11	0.49	-	-	-	-	0.03 ±0.04
Relative importance of variable					**0.00**	**0.13**	**0.00**	**0.00**	**0.11**

S2.2d) Growling/Screeching

K	AICc	ΔAICc	AICc Wt	Cum. Wt	Sex (M)	Season (Mating)	DFTD (+)	Years since DFTD	Nº Wounds
7	656.08	0.00	0.23	0.23	-	-	-	- 0.16 ±0.09	- 0.19 ±0.12
6	657.06	0.98	0.14	0.37	-	-	-	-	- 0.19 ±0.12
6	657.32	1.24	0.12	0.49	-	-	-	- 0.16 ±0.09	-
6	657.49	1.40	0.11	0.60	-	-	- 1.08 ±0.67	-	-
5	658.44	2.36	0.07	0.67	-	-	-	-	-
Relative importance of variable					**0.00**	**0.00**	**0.11**	**0.35**	**0.37**

Table S2.2 Parameter estimates for the preferred ordinal mixed models assessing biological and disease-related patterns of variation in a) urination/defecation, b) farting, c) huffing/jaw clomping and d) growling/screeching behaviours in Tasmanian devils. Models were ranked according to Akaike's Information Criterion corrected for small sample sizes (AICc); values for difference in AICc (ΔAICc) from the previous model, model weight (AICc Wt) and cumulative model weights (Cum. Wt) are displayed, along with the relative importance of each variable across the entire model set. Only models ranked above the null model are listed, in each case models failed to exceed a threshold of $\Delta AICc < 5$ from the null model. Individual identity was included as a random effect in each model.

Chapter 3

Rate of intersexual interactions affects injury likelihood in Tasmanian devil contact networks

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Image: Sébastien Comte

ABSTRACT

Identifying the types of contacts that result in disease transmission is important for accurately modelling and predicting transmission dynamics and disease spread in wild populations. We investigated contacts within a population of adult Tasmanian devils (*Sarcophilus harrisii*) over a six-month period and tested whether individual-level contact patterns were correlated with accumulation of bite wounds. Bite wounds are important in the spread of devil facial tumour disease (DFTD), a clonal cancer cell line transmitted through direct inoculation of tumour cells when susceptible and infected individuals bite each other. We used multi-model inference and network autocorrelation models to investigate the effects of individual-level contact patterns, identities of interacting partners, and position within the social network on the propensity to be involved in bite-inducing contacts. We found that males were more likely to receive potentially disease-transmitting bite wounds than females, particularly during the mating season when males spend extended periods mate-guarding females. The number of bite wounds individuals received during the mating season was unrelated to any of the network metrics examined. Our approach illustrates the necessity for understanding which contact types spread disease in different systems to assist the management of this and other infectious wildlife diseases.

Key-words: Contact network, Tasmanian devil facial tumour disease, disease transmission, infectious cancer, social network analysis, social behavior, transmission event

INTRODUCTION

Emerging infectious diseases (EIDs) are a major threat to biodiversity globally (De Castro and Bolker 2005; Smith et al. 2006). EIDs frequently impact populations that are already declining, thereby exacerbating the effects of habitat degradation, pollution, human-wildlife conflict or climate change (Blaustein et al. 2011; Heard et al. 2013). An increasing number of EIDs are recognized to cause severe population declines, including two species of chytrid fungus in amphibians (Stuart et al. 2004; Martel et al. 2014) and white-nose syndrome in bats (Blehert et al. 2009). The transmission processes by which infectious diseases spread through natural populations are not well understood, but their dynamics are underpinned by the behavior of individuals. Evaluating how contact patterns affect the transmission dynamics of infectious diseases within and among populations is an urgent priority for management of infectious disease and endangered species conservation.

Patterns of interaction among individuals have major consequences for disease dynamics of directly transmitted pathogens, including transmission, and the rate and spatial scale of spread (Kappeler et al. 2015; Arthur et al. 2017). In highly social species, such as group-living mongooses (Drewe 2010) and most primates (MacIntosh et al. 2012; Carne et al. 2014), individuals associate closely within social groups and groups interact regularly, often in territorial conflicts or out-breeding events (Madden et al. 2009; Weber et al. 2013). Regular interaction between group members facilitates rapid disease spread within groups, while inter-group contacts allow disease spread among groups and between populations (Craft et al. 2011). Patterns of disease transmission are more varied in solitary species, where interactions between individuals are less frequent, and the extent of the effect can be influenced by population size and density (Caillaud et al. 2006; Langwig et al. 2012). In solitary species, spread of pathogens (particularly those requiring direct contact for transmission) generally

occurs during specific events, such as mating (Ganguly et al. 2016) or competition over resources (Wright and Gompper 2005). In these cases, the familiarity of individuals may influence the likelihood of a successful transmission event (Vander Wal et al. 2012; VanderWaal et al. 2016; Hasenjager and Dugatkin 2017). For example, familiar individuals may have an established dominance hierarchy that seldom requires physical interaction. Consequently, unfamiliar individuals may be more likely to have physical confrontations (Brunton et al. 2008; Robinson et al. 2015), thereby heightening the chance of pathogen transfer. Thus, identifying the circumstances under which transmission is likely to occur is important for understanding disease dynamics, but can be difficult in cryptic species.

Social network analysis is increasingly used as a tool for understanding process flows through biological systems (Krause et al. 2007; Aplin et al. 2015; Craft 2015; Silk et al. 2017a; White et al. 2017) as it facilitates analysis of how contact patterns at the individual level, and network structures at the population level, influence transmission dynamics (Rushmore et al. 2013; Rimbach et al. 2015). Studies of information transfer (e.g. discovery of resource patches, novel foraging methods) have revealed patterns relating to networks both within and between species, and how these affect information flow (Aplin et al. 2012; Farine et al. 2012; Aplin et al. 2015; Firth et al. 2016). Emerging patterns that link an individual's centrality (the various properties of its position in a community; Borgatti 2005) within a network to its influence on transmission dynamics have been uncovered in multiple processes, particularly information flow (Aplin et al. 2012; Allen et al. 2013), parasite load (Godfrey et al. 2010; VanderWaal et al. 2014) and disease spread (Drewe 2010; Weber et al. 2013; Silk et al. 2018). Key metrics relating to transmission include *degree* (representing either the total number of interactions individuals have, or the total number of other individuals they interact with), *betweenness* (number of shortest paths between nodes in the

network that flow through an individual) and *clustering coefficient* (probability that an individual's neighbours are also well connected). For example, individuals that regularly engage in behaviors involving direct interactions (e.g. mate prospecting, grooming) will have high scores for degree metrics, while individuals that act as bridges between disparate groups are easily identifiable by high betweenness (Weber et al. 2013). Both tendencies inflate risk of pathogen transmission (Drewe 2010; MacIntosh et al. 2012) and can play key roles in transmission dynamics. In extreme cases, such individuals can be superspreaders (Lloyd-Smith et al. 2005) responsible for the majority of infections in a population, and thus those that are particularly important to identify as potential targets for intervention.

The Tasmanian devil (*Sarcophilus harrisii*) and its transmissible cancer, devil facial tumour disease (DFTD), provide an excellent study system to quantitatively assess infection risk using contact networks. Devils are under threat from DFTD, which is transmitted when live tumour cells, the pathogenic agent (Pearse and Swift 2006), are transferred from infected to susceptible individuals when they bite one another (Hamede et al. 2013). Individuals that develop DFTD almost invariably die within 6-12 months of clinical symptoms appearing (Loh et al. 2006; Hamede et al. 2012; Wells et al. 2017). The key to understanding the transmission dynamics of DFTD and modelling its spread is establishing the patterns of contact that result in bite wounds (Hamede et al. 2013). In devils, the most common type of contacts, such as those between individuals with overlapping home ranges (Guiler 1970) and at regular aggregations around food sources (Pemberton and Renouf 1993), are most likely to be benign with little or no injurious biting. However, observing interactions that may be linked to disease spread is difficult since devils are cryptic and nocturnal, with some behaviors linked to injuries (such as mating) occurring in their underground burrows. Using proximity loggers (radio-collars capable of logging when individuals come in close

proximity) to investigate contact networks in wild devils, Hamede et al. (2009) found that all devils in a population were connected in a single network and that contact frequencies were higher during the mating season, but the relationship between contact rates and the likelihood of being bitten was not assessed.

In this study, we examine contact patterns and bite wound accrual simultaneously in a DFTD-free wild population of Tasmanian devils using proximity loggers coupled with regular captures. Through multi-model inference, we investigate contact patterns among individuals, their position in the social network and propensity to accumulate bite wounds. We explore the effect of sex and familiarity of contact partners on the likelihood of receiving bite wounds, which constitute potentially disease-transferring contacts. Understanding the identity and interaction patterns of those individuals likely to be involved in disease transmission events could guide management of DFTD spread in populations not yet affected by the disease. These analyses afford a new perspective on the potential of different types and contexts of social contacts to transmit disease in a wild population.

MATERIALS AND METHODS

Proximity loggers

We used proximity data loggers fitted to adjustable collars (Sirtrack E2, Havelock North, New Zealand) to record interactions between devils. Each logger emits a unique UHF pulse so that when two, or more, loggers are within a pre-determined distance of one another (calibrated via UHF detection range) the time, date, encounter length and unique logger number(s) are recorded and stored on the internal memory of the device. Collars also incorporated a VHF component, on a separate circuit and battery, so the animals could be located. The entire collar assembly weighed 120g – less than 2.5% of the body weight of the smallest individual collared.

To ensure that only contacts with the potential to lead to DFTD transmission were recorded, loggers were calibrated to detect and interrogate one another at a distance of 30 cm or less. This represents the physical distance at which devils could conceivably bite one another, and hence transfer disease (see Hamede et al. 2009 and Hamede et al. 2013 for further rationale). Loggers were programmed to have a separation time of 10 seconds, meaning that a single encounter was recorded by each device until they had failed to detect one another for a period of 10 seconds or more, as is consistent with previous research (Hamede et al. 2009). Prior to deployment in the wild, detection distances for each individual collar were calibrated and then tested in a laboratory setting, as well as with captive devils at Bonorong Wildlife Sanctuary (see Supplementary Materials 3.1 for details of each collars performance).

Upon collar retrieval, data from each individual were filtered to ensure that there was symmetry between collar data for each dyad. For all interactions greater than one second that were logged by both collars in a dyad we took the time between when the first collar

commenced logging and when the last collar terminated logging as the interaction duration. Contacts of one second duration were eliminated from the dataset, as these represent "phantom contacts" – the result of collars being just outside detection range and incorrectly decoding faint signals as contact events (Prange et al. 2006).

As all individuals were fitted with collars for slightly different time periods (all animals were collared on different days, while 3 individuals died as a result of vehicle collision during the study period) all terms relating to interactions were calculated as rates as opposed to absolute numbers. For each dyad between animals their interaction rate was calculated as the total number of interactions within the dyad divided by the number of days that both individuals were collared concurrently. This resulted in an interaction rate for each pairing of individuals, which were then summed to calculate each individual's total interaction rates with different classes of interaction partners; the rate for each dyad was used as an edge between interaction partners during network calculations. This standardisation of interaction rates accounts for slight differences in sampling effort between individuals (Farine and Whitehead 2015; Blaszczyk 2017)

Study site and data collection

The study was conducted in the northern section of the Arthur Pieman Conservation Reserve, north of the Arthur River, in north-western Tasmania (-40.999 E, 144.649 S). The population was not affected by DFTD throughout the study period. Habitat in this area predominantly consists of coastal scrub and eucalypt forest dominated by *Eucalyptus obliqua* and *E. nitida*.

Tasmanian devils were caught for collaring by setting 35 traps over a 25 km^2 area for a period of one month. Traps were custom built of 300 mm polypipe and baited with a variety

of meats. The population of devils used for the study had been surveyed regularly for two years prior; therefore, we had previous knowledge of which individuals were resident and which were vagrants (see Supplementary Materials 3.2 for details of the background population). All sexually mature devils (two years of age and older) trapped in the study area with a trap history that indicated they were residents of the core area were fitted with collars between January and March 2015 (12 females, 10 males). Geographical barriers to the south (the deep and 20 - 100m wide Arthur River), east (wide tracts of open paddock) and west (the Indian Ocean) limit movement of new adult individuals into the population. Proximity collars were activated and collecting contact data on devils from January until the end of June 2015. This timespan encompasses both mating (February to April) and non-mating periods (May to June), so differences in contact rates between reproduction-relevant seasons could be assessed, with 22 animals available for the non-breeding season and 20 in the breeding season. The timing of the mating season was determined by backdating birth date and pregnancy based on the developmental stage and size of pouch young (see Hesterman et al. 2008 and Hamede et al. 2009 for further details).

Collared devils were re-trapped monthly throughout the study period to document new wounds as they occurred, as well as to assess collar fit. Only wounds that penetrated the dermis were recorded, as these are the injuries that have the potential to result in DFTD transfer. The period between captures of each individual was generally a month or less, meaning that new wounds were unlikely to have healed between captures (penetrating wounds in Tasmanian devils take three to eight weeks to heal to a point at which they are undetectable, depending on their severity). Positions of wounds on the animal were recorded and photographed on each capture so that new wounds could be identified on future captures (see Supplementary Materials 3.3 for examples). Since agonistic interactions with other

predators (spotted-tailed quolls, *Dasyurus maculatus*, and feral cats, *Felis catus*) are extremely rare (Jones 1995), all wounds recorded are likely to have come from conspecifics.

Network construction and statistical analyses

Contact networks were constructed in the *igraph* package in R v3.2.5 (R Core Team 2018) using the filtered contact rate in each dyad. Networks were separated into mating (15th February - 15th April) and non-mating (Jan – 15th February and 15th April – 30th June) seasons. Individuals were represented as nodes linked by observed contact rates. The size of nodes represented the number of wounds individuals received over the course of each season, while lines between nodes (edges) were weighted by the rate of contacts. Network metrics and properties (detailed later) were also calculated using *igraph*.

We investigated the relationship between individual interactions and the number of wounds that devils accumulated over the course of the study for all 22 devils in the adult population. We used generalized linear mixed models (GLMMs) with Poisson error to assess the effects of the number of bite wounds on two categorical variables (sex and season) and four continuous variables describing modes of interactions: 1) rate of interactions of less than one minute, 2) rate of interactions of more than one minute, 3) proportion of hours spent in extended pairings with opposite sex and 4) proportion of hours spent in extended pairings with the same sex). Interactions totalling less than one minute represent brief contacts, where individuals come into close proximity for a short period, while interactions totalling more than one minute represent prolonged interactions. The hours spent in extended pairings with the opposite sex represent two devils sharing a den in close proximity. Regular physical confrontation can occur during these periods, which last from 1 – 13 days as males attempt to restrain females from departing during their oestrous. Hours spent in extended pairings with

the same sex represent intra-sex den sharing – it is likely that these events represent devils tolerating each other's presence, although physical aggression could occur during such encounters. To account for small sample size (n = 22 individuals over two seasons), we included no more than three independent variables per model and no more than five models in each analysis. Based on *a priori* knowledge (Hamede et al. 2013), and clear patterns in the results, that a) devils acquire more wounds in the mating season, and b) males acquire more wounds than females (see Figure 3.2), the categorical variables accounting for sex and season (and an interaction term between them) were retained in the majority of models. Each model contained one random factor, individual, to account for the models including data separated into seasons (mating and non-mating) for each individual. The null model contained only the random factor.

We developed model hypotheses related to the factors potentially influencing biting contacts (and therefore potential transmission of DFTD) in devils, to derive the best prediction of the number of bite wounds an individual received over the course of the mating and non-mating seasons. We used a multi-model inference approach (Burnham and Anderson 2002), ranking models using Akaike's Information Criterion corrected for small sample size (AICc). All models were run using the *lme4* and *AICcmodavg* packages in R v3.2.5 (R Core Team 2018). See Supplementary Materials 3.4 for a list of all models run.

We then investigated the relationship between the identity of an individual's interaction partners and the number of bite wounds it received in a further set of GLMMs (using the same multi-model inference approach and packages as detailed above). For this analysis, we measured the effect of the regularity with which an individual interacted with their dyadic partners, as well as the sex of those dyadic partners, on the number of bite wounds they

received. To quantify the regularity of contact with interaction partners, each dyad was ranked as "*weak"* (rate of 0 to 0.1 interactions per day), "*intermediate"* (rate of 0.1 to 0.5 interactions per day) or *"strong"* (rate of > 0.5 interactions per day) ties. These represent the regularity of contact between pairs of individuals and may affect likelihood of involvement in a physical interaction with one another. Analyses were run using both more and less generous cut-off frequencies for "*weak*" (rate of 0.05 through 0.4 per day), "*intermediate*" (rate of 0.05 through 1 per day) and "*strong*" (0.5 through 2 or more per day) dyads, but patterns remained identical at the varying thresholds. The dyadic ranking thresholds used in the final models divide the observed data into three approximately equal groups. We assessed the effects of two categorical variables (sex and season) and five continuous variables (rate of interactions in "*weak*" dyads, rate of interactions in "*intermediate*" dyads, rate of interactions in "*strong*" dyads, rate of interactions with males and rate of interactions with females) on the number of bite wounds acquired by individuals. The same random factor (individual) as in the previous set of models was included in all models, including the null model.

Finally, to establish the influence of an individual's position within a network (network metrics) on its propensity to pick up bite wounds, we applied network autocorrelation models (NAMs; R package *tnam*) to the contact networks for mating season and non-mating season respectively. In each model, sex and age were fitted as fixed effects, while terms were fitted for social network metrics which are likely to have an influence on disease transmission, specifically: 1) weighted degree (the proportion of individuals in a population that an individual associates with); 2) betweenness centrality (the number of shortest paths that flow through a node); 3) closeness centrality (metric based on the sum of shortest paths that run through a node); and, 4) clustering coefficient (measure of how many of a node's connections are also connected). None of these network metrics were significantly correlated with one

another. Each network term was centred, while the inherent non-independence of connected individuals in the network was accounted for using a *weightlag* term in the model. All network centrality measures examined provide indications of how influential an individual will be in the event of disease spreading through a population. If these metrics relate to the number of potentially disease-causing bite wounds an individual receives, they provide a proxy for the role of that individual in DFTD transmission in the case of an outbreak. We also tested for differences in bite wounds and social network metrics between sexes and seasons using node-permuted t-tests, comparing to 10,000 randomized t-statistics to account for non-independence (Croft et al. 2011).

RESULTS

The total number of interactions recorded was 8,854 (7,126 in the mating season, 1,728 in the non-mating season), and the network metrics and wounds are summarized in Table 3.1. The mean number of bites received per individual was 6.15 (S.E. = 1.17) in the mating season and 2 (S.E. = 0.53) in the non-mating season (Table 3.1). Contact networks were comprised of one large component (i.e. all individuals were connected, either directly or indirectly) during both the mating and non-mating seasons (Figure 3.1). Number of wounds received by devils differed significantly between seasons ($P = 0.005$; paired t-test), and between sexes during the mating season ($P = 0.026$), with a higher number of wounds received by males, particularly during the mating season (Figure 3.2). The only network metrics which differed between seasons were closeness centrality, which was significantly higher during the mating season ($P = < 0.001$), and clustering coefficient, which was significantly higher during the non-mating season, particularly in females ($P = 0.019$; Table 3.1).

	Mating season			**Non-Mating Season**		
Network measures	**Females**	**Males**	**Both sexes**	**Females**	**Males**	**Both sexes**
N	11	9	20	12	10	22
Wounds	**3.55 ± 0.62**	**9.33 ± 2.09**	**6.15 ± 1.17**	2.25 ± 0.77	1.70 ± 0.73	**2.00 ± 0.53**
Degree	7.36 ± 0.73	7.00 ± 1.05	7.20 ± 0.61	7.58 ± 1.07	9.10 ± 1.16	8.27 ± 0.78
Betweenness	14.25 ± 4.38	12.62 ± 4.90	13.52 ± 3.18	13.05 ± 3.14	16.45 ± 4.67	14.59 ± 2.68
Closeness	0.019 ± 0.0009	0.019 ± 0.001	**0.019 ± 0.0007**	0.012 ± 0.0008	0.013 ± 0.0005	**0.012 ± 0.0005**
Clust. Coef.	0.48 ± 0.04	0.40 ± 0.06	**0.44 ± 0.04**	0.64 ± 0.06	0.54 ± 0.05	**0.60 ± 0.04**

Table 3.1 Mean (± S.E.) network metrics based on interaction rates by sex and season. Values of metrics which alter significantly ($p < 0.05$) between females and males within seasons, and between all individuals between seasons are in bold.

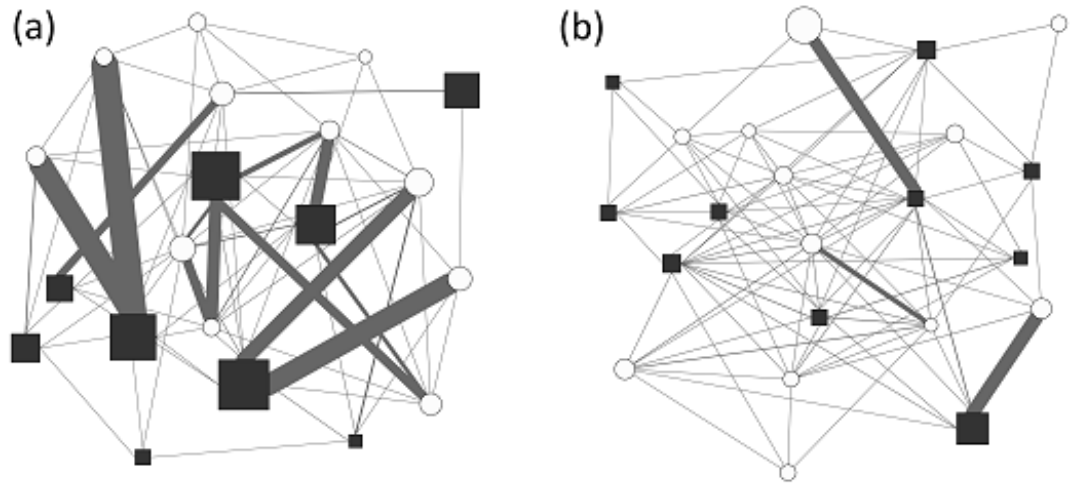

Figure 3.1 Contact networks based on rate of associations between individual Tasmanian devils during (a) mating season and (b) non-mating season. Black squares represent males, while white circles represent females – node size represents how many wounds an individual accumulated during the season (0 – 17 wounds). Edges between nodes represent interaction rate within the dyad – the thicker the line, the higher the rate of interaction between that pair of individuals.

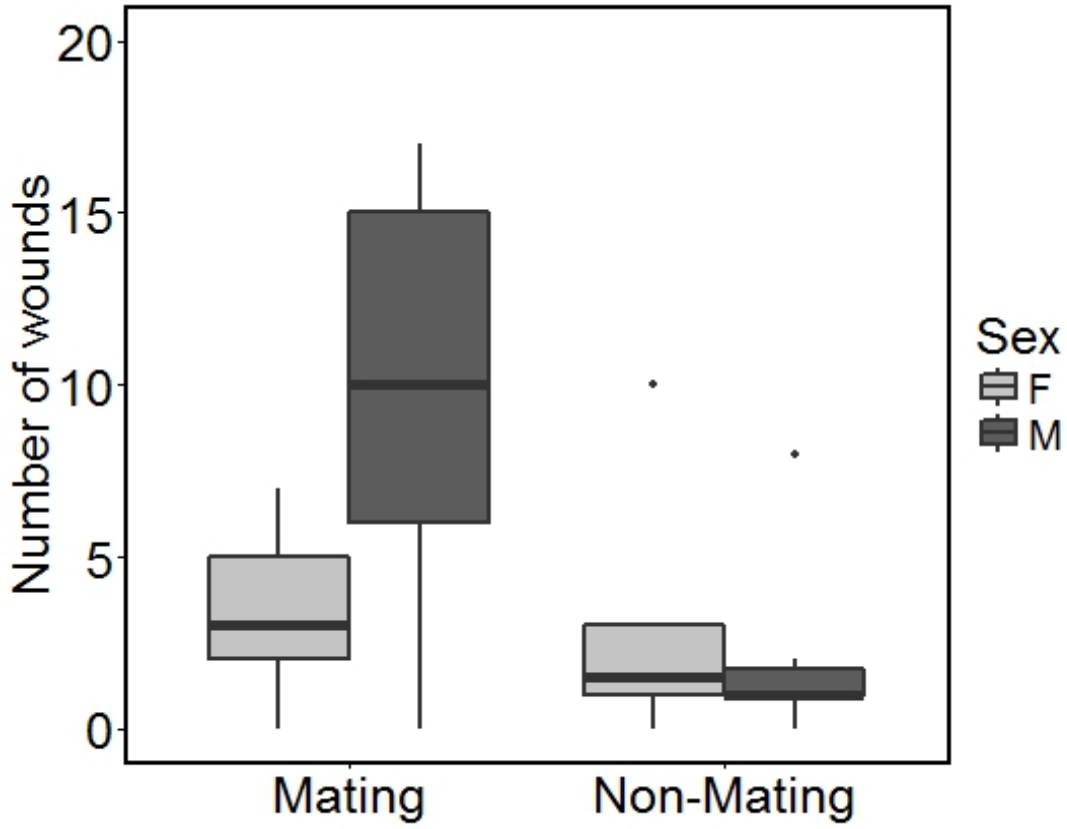

Figure 3.2 Boxplot of the number of wounds accumulated by female and male Tasmanian devils over the course of the mating and non-mating periods. Lines across boxes indicate medians, while box boundaries represent interquartile ranges. Whiskers identify data points no more than 1.5 times the interquartile range on either side; points outside the whiskers represent extreme outliers outside this range.

Influence of individual interactions

The most important predictor of the number of bite wounds received was the proportion of hours an individual spent in extended intersexual contacts. This effect was sex specific. Under the single best fitting model males accrued one additional bite wound for every 42.59 hours spent in extended intersexual contacts in the breeding season; no pattern was apparent for females. This model, which accounted for 81% of AICc weight, included this factor alongside the categorical variables sex and season (see Table 3.2a). A second model (incorporating rate of contacts of less than one minute, sex and season) was separated from the first model by just over three units of AICc (ΔAICc = 3.08) and accounted for 17% of AICc weight (see Table 3.2a). Other models had much greater steps in AICc.

Influence of interaction partners

The more time male devils spent in strong dyads, the more likely they were to accumulate bite wounds. The best supported model in the analysis of influence of dyad partners contained the factors strong ties (interaction rate of > 0.5 per day), sex and season, and accounted for 93% of AICc weight (see Table 3.2b). A second model, explaining 7% of AICc weight (ΔAICc = 5.05), contained the number of contacts with female interaction partners. The models containing weak and intermediate ties received no support (see Table 3.2b).

a)

K	AICc	ΔAICc	AICc Wt	Cum. Wt	Sex	Season	Hours O.S.	Hours S.S.	< 1min	> 1min
7	199.95	0	0.81	0.81	0.69 ± 0.21	0.04 ± 0.27	0.15 ± 0.03	—	—	—
7	203.03	3.08	0.17	0.98	0.80 ± 0.22	0.02 ± 0.28	—	—	0.06 ± 0.01	—
7	207.30	7.35	0.02	1.00	0.83 ± 0.25	- 0.12 ± 0.27	—	—	—	0.20 ± 0.06
Relative importance of variable					**1.00**	**1.00**	**0.81**	**0.00**	**0.17**	**0.02**

b)

K	AICc	ΔAICc	AICc Wt	Cum. Wt	Sex	Season	Weak	Intermediate	Strong	Male	Female
7	203.43	0	0.93	0.93	0.80 ± 0.23	0.006 ± 0.28	—	—	0.05 ± 0.01	—	—
7	208.48	5.05	0.07	1.00	0.39 ± 0.27	- 0.41 ± 0.25	—	—	—	—	0.04 ± 0.01
7	222.02	18.60	0.00	1.00	1.52 ± 0.39	0.04 ± 0.35	—	—	—	0.05 ± 0.03	—
Relative importance of variable					**1.00**	**1.00**	**0.00**	**0.00**	**0.93**	**0.00**	**0.07**

Table 3.2 Results of GLMM's showing the influence of an individual Tasmanian devil's a) interactions and b) interaction partners in predicting the number of bite wounds it acquires. The model number, Akaike's Information Criterion corrected for small sample sizes (AICc), difference in AICc (ΔAICc), model weight (AICc Wt), cumulative model weights (Cum. Wt) and parameter estimates for model variables (including standard errors) for each GLMM run on interaction patterns using a multi-model inference approach. The relative importance of each variable is indicated as the sum total of the model weights across the entire model set for each variable. Only the top three models are listed, unless a higher number than this fail to exceed a threshold of ΔAICc < 5.

Influence of network position

None of the network metrics examined provided a strong predictor of the number of bite wounds an individual received. The only factor found to influence number of bite wounds accrued was the sex of the individual, again with males more likely to obtain bite wounds in the mating season (see Table 3.3). Similarly, none of the network metrics examined proved to be a strong predictor of the number of bite wounds accrued in the non-mating season (see Table 3.3).

Mating Season

Model term	Estimate	S. E.	Z value	P value
Intercept	- 3.702	3.197	- 1.158	0.266
Sex	6.105	2.124	2.874	0.012*
Degree	- 0.031	0.745	- 0.042	0.967
Betweenness	0.072	0.149	0.486	0.635
Closeness	34.280	22.559	1.520	0.151
Clustering Coef.	- 7.605	39.362	- 0.193	0.850

Non-Mating Season

Model term	Estimate	S. E.	Z value	P value
Intercept	1.627	1.802	0.903	0.380
Sex	- 0.431	1.185	- 0.364	0.721
Degree	0.337	0.308	1.095	0.290
Betweenness	0.014	0.083	0.173	0.865
Closeness	21.243	14.919	1.424	0.174
Clustering Coef.	16.559	33.564	0.493	0.628

Table 3.3 Results of Network Autocorrelation Models run on mating and non-mating season Tasmanian devil networks. Models examined the number of wounds received as an outcome of individual sex, while also controlling for non-independence of measures to quantify the effect of network position measures of degree, betweenness, closeness and clustering coefficient.

DISCUSSION

Identification of potential disease transmission events, and their occurrence within contact networks, is critical for understanding the dynamics of disease spread (Craft 2015; Chen and Lanzas 2016; Manlove et al. 2017). Here, we conducted a contact network study in Tasmanian devils while simultaneously examining potential disease transmission events. Divergences between sexes and seasons were identified which are likely to have significant consequences for the spread of disease in Tasmanian devils. Males acquired more dermis-penetrating bite wounds with the potential to facilitate DFTD transmission than females, and these occurred mostly during the mating season. Acquisition of bite wounds in males was highly correlated with time spent in extended contacts with females, particularly those with whom they interacted regularly. These results contribute to our understanding of disease susceptibility and how it relates to variations in contact patterns between individuals (Altizer et al. 2006; Blyton et al. 2014; Han et al. 2015).

Our use of proximity loggers indicated that the mating season wounds received by males were associated with extended associations with females (lasting 1-13 days), shedding doubt on a previously held perception that the large number of injuries in males during the mating season result from male—male combats aimed at accessing females (Hamede et al. 2008). Mate guarding behavior is seen in devils (Jones, *unpublished*) and a variety of other species (Taggart et al. 2003), and involves males attempting to exclude other males from access to a female in oestrous to increase the guarder's chance of paternity. Guarding behavior can involve high levels of aggression towards competing males (Girard-Buttoz et al. 2014; Baxter et al. 2015) and can also be associated with aggression between the male and the female being guarded (Elias et al. 2014), including in devils (Jones, *unpublished*). However, male—male interactions were rare during the mating season and their rate of occurrence was not

associated with frequency of injuries. This result corroborates the findings of Hamede et al. (2009) that devil mixing patterns during the mating season were almost entirely intersexual. Our additional examination of the bite wounds devils accrued whilst involved in interactions with other devils has allowed insights into the potential of these associations to result in disease transfer. Our results suggest that males are being wounded while guarding females in oestrus, and the longer they spend engaged in this type of behavior, the more wounds they receive. This highlights the potential for mating interactions to enhance disease transmission and is consistent with recent findings that Tasmanian devils with a high reproductive output are more likely to contract DFTD during their lifetime (Wells et al. 2017). Use of proximity collars has provided new insights into the mating behavior of devils, a cryptic, nocturnal species that is difficult to observe directly in the wild, particularly mating interactions that usually occur in underground burrows.

Network structure and contact rates between devils were comparable with a previous study (Hamede et al. 2009). In both studies, networks for the mating and non-mating seasons were comprised of one large component, male-male interactions were relatively rare and extended male-female interactions made up the bulk of contacts during the mating season. While values for degree and betweenness were higher in the 2009 study (see Hamede et al. 2009 and Table 3.1), network density was comparable, indicating divergences can likely be attributed to the higher number of nodes in the earlier networks. This suggests that large scale patterns observed in devil networks, particularly pertaining to the mating interactions that are potentially critical to disease transfer, are relatively consistent between populations.

Given that a high proportion of potentially disease-transmitting bite wounds occurred during the mating season, particularly during mate-guarding, how does this compare to observations

of patterns of the transmission of DFTD? Unfortunately, the disease does not have a consistent latent period, with the limited information available on time from transmission event to development of clinical signs ranging from 3 weeks (in experimental trials) to 11 months in the wild (asymptomatic individual developing tumours after being brought into captivity). This variability in latent period obscures any potential seasonality in the transmission of the disease (Hamede et al. 2009; McCallum et al. 2009). Additionally, there is no evidence from extensive mark-recapture data that DFTD prevalence differs between the sexes (Hawkins et al. 2006; McCallum et al. 2009; Hamede et al. 2012; 2015). This lack of sex bias in disease prevalence seems to contradict our results, which indicate that males are more likely to obtain potentially disease-transmitting wounds. However, most injuries to males were associated with their interaction rate with females rather than males, which supports a lack of sex bias in disease prevalence. Outside of the mating season, the rate of biting injuries and most network metrics are more even between the sexes and the rate of injurious biting is lower than that during the mating season. However, cumulatively over the course of the year the number of injuries is still substantial and likely to have an influence on DFTD transmission. Notably, both sexes display heightened levels of clustering (meaning they are well connected to other well-connected individuals within the network; see Figure 3.1 and Table 3.1) outside the mating season, which may increase their probability of coming into contact with diseased individuals (even though their total number of potentially disease-causing interactions is lower). This additional potential for exposure to diseased individuals outside the mating season would result in DFTD continuing to spread through the population even during periods when the seemingly critical mating interactions are not occurring. Further studies of the contact patterns of devils in DFTD-affected populations are required to identify additional vulnerable periods throughout the year and to fully explain the lack of sex bias observed in DFTD prevalence.

In terms of relating our findings to real time transmission of DFTD in the wild, there is uncertainty concerning the dominant direction of disease transfer. Transmission could occur by devils biting the tumour of another animal, or by having live tumour cells inoculated when they are bitten. Empirical data support the former possibility, as devils that have fewer bite wounds are more likely to acquire the disease (Hamede et al. 2013). This led to the hypothesis that more dominant animals were biting subordinate animals, possibly into their tumours, and becoming infected (Hamede et al. 2013), which appears consistent with results suggesting individuals with higher reproductive success were more likely to acquire DFTD (Wells et al. 2017). The results presented here, and observations of devil mating behavior in captivity (Jones, *unpublished*), suggest that both sexes bite each other during mating interactions, but females cause a higher number of injuries (to the males) during the mating season, when there is also an annual peak in biting injuries (Hamede et al. 2013). Insights into cryptic devil behavior are beginning to overturn our assumptions about male dominance in aggressive encounters and suggests that males could be critical to transmission dynamics during the mating season, as they are involved in high numbers of interactions as either the potential vector or recipient of DFTD cells. However, it remains unclear what proportion of transmission incidences result from biting or from being bitten. A combination of both forms of transmission would reconcile the lack of sex bias in DFTD prevalence with our results. Further understanding of the directionality of disease transfer is required before we can fully ascertain how DFTD travels through devil populations.

Unequivocally identifying causal relationships between disease transmission and the structure of the contact network would require matching network parameters with patterns of acquisition of infection as disease moves through a population. Our conclusions are based on the behavior of Tasmanian devils that are disease-free, but disease infection may alter

behavioral contacts, and alter transmission pathways. Both short-term behavioral changes resulting directly from symptoms of infection and long-term changes due to differential survival of more or less interactive individuals are possible. Therefore, such insight will be possible only by conducting a similar study in a population of Tasmanian devils recently infected with DFTD. Prior to this being achieved, our study has successfully shown an association between contact patterns and propensity to engage in injury causing aggressive encounters. Specifically, our results strongly suggest that males engaged in mate guarding during the mating season may be particularly important in the transmission of DFTD, either as recipients or transmitters of infection.

A lack of detailed knowledge of contact patterns is a major issue in both the management of wildlife diseases and attempts to model future outbreaks. Even in populations that have been well-monitored, or in cases where clinical symptoms of infection are obvious, it is notoriously difficult to pinpoint incidences of disease transfer (Drewe 2010; Craft 2015; Manlove et al. 2017). Where contacts or interaction patterns are studied in detail, transmission rates are often found to be influenced by factors including season, behavioral tendencies and temporality (Blyton et al. 2014; Langwig et al. 2015; Silk et al. 2017c). These variations at the individual level are important to parameterize accurate and realistic disease models (Craft and Caillaud 2011). New technologies and methodologies are allowing more detailed insights into seasonal, or even daily, variations in patterns of contact between individuals (Silk et al. 2017b). Highlighting these fine scale details is critical to our understanding of disease spread, as it allows a closer examination of the role individuals play in epidemics (Tompkins et al. 2011). Crucially, identifying specific transmission events will allow the transition from creating contact networks, to developing transmission networks, based exclusively on contacts that actively transmit disease (Chen and Lanzas 2016).

Development of such a network for DFTD will allow better understanding of how this novel cancer has disseminated across most of the distributional range of the species and how its future spread to unaffected populations might be managed. Similar network transitions in studies of disease outbreaks in other species and communities will extend our knowledge of disease ecology as well as improving the containment and management of potential future outbreaks.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *Behavioral Ecology* online.

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DATA ACCESSIBILITY

Analyses reported in this article can be reproduced using the data provided by Hamilton et al. (2019).

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SUPPLEMENTARY MATERIALS – CHAPTER 3

Supplementary Materials 3.1 *Proximity Logger Calibration*

Prior to deploying proximity loggers on wild devils, we undertook both laboratory and field trials to test their performance. All collars were initially set to a UHF power setting of 7, which provided a detection threshold of approximately 30cm. However, as collars can vary in sensitivity (due to structural factors which can vary slightly in individual collars, such as thickness of epoxy material) we tested the detection distance of each collar to ensure their detection distances were consistent. Pairwise combinations of all collars (N = 25) were randomly chosen for testing of detection distance in the laboratory. Each collar was placed on a horizontally oriented bottle containing 2L of saline solution (this mimics the UHF absorption of a medium-sized mammal, to control for the potential conductive properties of being on the animal itself). Collars were then slowly moved towards one another; the distance at which they began to log one another was recorded for each unit. Once both collars had commenced logging, they were moved apart and the distance at which logging was terminated was recorded. This procedure was repeated multiple times, until each collar unit had been involved in 3 pairwise trials. Any collars which persistently displayed detection/termination distances significantly different to 30cm were adjusted until their distances were equivalent to other units over 3 pairwise trials (2 collars had to be adjusted in this way, though neither ended up being used in the final study). The average detection and termination distance for each unit is displayed in Table S3.1.

Collar Nº	Mean Initiation distance (cm)	Mean termination distance (cm)
2	37	43.33
3	37	38
4	27.67	31.33
5	26.67	32.67
6	31.67	36.67
7	32	34.67
9	26.33	33.33
10	28.67	33
12	28.33	35.33
13	32.33	38.67
15	35	45
16	32.67	35.33
17	28	33.67
18	34	38.67
19	28	32
23	26.67	30
25	29	34.67
26	26.67	31.33
27	28.67	35.33
28	26.33	33.33
29	26.67	35.33
30	28	30
31	29.67	33.33
32	28.33	36
35	32.33	38

Table S3.1 Mean initiation and termination distances (cm) for interaction logging in 25 proximity loggers tested in laboratory trials of detection distances.

In addition, laboratory trials were conducted with pairwise combinations of all collars to measure consistency of recorded interaction duration between collars. In each trial two collars were left within 30cm of one another for a pre-determined period, then separated. The duration each collar had recorded the interaction as lasting was noted for each collar, and the difference in seconds calculated. These trials were repeated with 15 pairwise combinations of collars for interaction durations of 5 seconds, 10 seconds, 30 seconds, 60 seconds and 30

minutes. Average differences in recorded interaction durations within pairs are displayed in Table S3.2.

Trial	Number	Average difference (sec)
5 sec	15	1.2 ± 0.20
10 sec	15	2.2 ± 0.54
30 sec	15	3.5 ± 1.16
60 sec	15	3.2 ± 0.78
30 mins	15	9.2 ± 2.91

Table S3.2 Mean differences in logged interactions between pairwise combinations of collars used in laboratory trials of pre-determined interaction durations – 5, 10, 30 and 60 seconds, and 30 minutes.

Field trials were undertaken using captive devils at Bonorong Wildlife Sanctuary. Proximity loggers were fitted to two, three and four devils simultaneously and collared devil interactions were recorded by an observer (DH) while feeding on a prey species carcass. A stopwatch was used in field trials to record encounter duration when devils were within 30cm of one another (a large black and white measuring stick was set in the background to assist with identifying distances in the field). In field trials, all collars successfully detected one another at distances of 25-35cm and terminated logging interactions at 35-45cm.

Supplementary Materials 3.2 *Background Population at Study Site*

Name	Microchip	Sex	Y.o.B	Times caught (Jan-Jul 2015)	% months caught	Collared?
Stumpy	982 000 190 530 299	M	2011	10	85.71	Yes
Evelyn	982 000 190 524 289	F	2011	6	57.14	Yes
Arya	982 000 190 698 298	F	2012	5	71.43	Yes
Larissa	982 000 190 701 413	F	2012	8	100	Yes
Cora	982 000 190 559 688	F	2011	4	57.14	Yes
Phoebe	982 000 190 607 189	F	2011	15	100	Yes
Linus	982 000 190 700 395	M	2012	18	100	Yes
Sansa	982 000 190 529 902	F	2012	6	100	Yes
Benbecula	982 000 363 022 229	M	2013	6	85.71	Yes
Andromede	982 000 356 574 811	F	2012	4	57.14	Yes
Pluto	982 000 190 524 534	M	2011	4	57.14	Yes
Arran	982 000 190 698 042	M	2013	12	100	Yes
Agamemnon	982 000 190 700 308	M	2011	19	100	Yes
Hermione	982 000 190 699 556	F	2010	18	100	Yes
Gail	982 000 356 584 120	F	2012	6	85.71	Yes
Mull	982 000 362 816 812	M	2013	11	100	Yes
Rambo	982 000 190 524 181	M	2011	4	57.14	Yes
Jocasta	982 000 356 584 215	F	2011	5	71.42	Yes
Cassandra	982 000 190 522 149	F	2011	11	100	Yes
Narcissus	982 000 190 532 851	M	2010	5	71.42	Yes
May	982 000 362 826 534	F	2013	16	100	Yes
Priam	982 000 190 608 407	M	2012	9	85.71	Yes
Bluebell	982 000 356 707 539	F	2013	3	42.86	No
Orkney	982 000 190 698 042	M	2013	3	14.29	No
Hebrides	982 000 363 022 077	M	2013	2	28.57	No
Hector	982 000 190 524 233	M	2010	2	28.57	No
Scarba	982 000 363 826 339	M	2011	1	14.29	No
Miss Houdini	982 000 356 571 014	F	2011	1	14.29	No
Soay	982 000 356 429 526	M	2013	2	14.29	No
Ulva	982 000 356 574 986	F	2013	2	28.57	No
Scarr	982 000 362 004 630	M	2010	2	14.29	No
Panda	982 000 362 005 223	F	2012	2	28.57	No
Henrietta	982 000 190 532 797	F	2010	1	14.29	No
Tilly	982 000 356 582 523	F	2013	1	14.28	No

Table S3.3 List of all adult (2+) Tasmanian devils caught in the 25 km^2 study area over the course of the 7-month collaring study, the number of occasions they were trapped and the proportion of study months in which they were trapped. None of the devils which were not collared had been caught in the study area prior to January 2015 (over 2 years of regular

trapping) and were highly likely to be vagrants which were not interacting regularly with any of the collared animals.

Supplementary Materials 3.3 *Wound Recording*

Every time a devil was trapped during the study period (January 2015 to July 2015) all externally visible wounds were recorded on a diagram, numbered and photographed (see Fig. S3.1). On subsequent captures, reference to these records allowed us to establish whether wounds were old and yet to heal fully, or new wounds received in the period between captures.

Figure S3.1 Sample pictures of wounds recorded on Tasmanian devils. Pictures 1a and 1b show a laceration on a female devil's chin which had begun to heal in the 8 day period between captures. Pictures 2a and 2b show a more substantial wound on a male devil's nose, where a piece of flesh was torn away. In the month between 2a and 2b the wound had not healed fully, but reference to capture records ensured it was not recorded as a new wound.

Supplementary Materials 3.4 *List and Hypotheses for all GLMMs*

Analyses	Model Nº	Parameters	Hypothesis / Rationale
Interactions	*1)*	Sex + Season + Hours_OS	Males receive most wounds, linked to extended inter-sex contacts in mating season
	2)	Sex + Season + Hours_SS	Males receive most wounds, linked to extended intra-sex contacts in mating season
	3)	Sex + Season + Less_1min	Males receive most wounds, linked to high frequency of short (< 1 min) contacts in mating season
	4)	Sex + Season + More_1min	Males receive most wounds, linked to high frequency of long (> 1 min) contacts in mating season
	5)	Sex + Season	Males receive most wounds during mating season, but this has no association with their interaction patterns
	Null	(Individual) + (Time collared)	
Dyad partners	*1)*	Sex + Season + Weak	Males receive most wounds, linked to high frequency of interactions with weak associates in mating season
	2)	Sex + Season + Medium	Males receive most wounds, linked to high frequency of interactions with medium associates in mating season
	3)	Sex + Season + Strong	Males receive most wounds, linked to high frequency of interactions with strong associates in mating season
	4)	Sex + Season + Male	Males receive most wounds, linked to high frequency of interactions with males in mating season
	5)	Sex + Season + Female	Males receive most wounds, linked to high frequency of interactions with females in mating season
	Null	(Individual) + (Time collared)	

Table S3.4 List of general linear mixed models (GLMMs) run to examine the effects of interactions patterns and dyad partners on an individual's propensity to pick up bite wounds. Parameters and hypothesis/rationale are listed for each model.

Chapter 4

Predicting DFTD spread through a naïve population of Tasmanian devils using contact- and transmission-based network models

Prepared for submission to *Journal of Applied Ecology* as:

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Image: Catherine Young

ABSTRACT

Simulation models based on accurate disease dynamics and contact patterns are important to our understanding and management of wildlife diseases. Recent improvements in telemetry have allowed collection of fine-scale data on contact heterogeneities for parameterising network models. As a result, in some systems, there is the possibility of parameterising and contrasting epidemiological models based on two types of contact data: contact networks and transmission networks. In this study we collected data from a wild Tasmanian devil (*Sarcophilus harrisii*) population and used it to parameterise simulation models of devil facial tumour disease (DFTD) spread based on both types of network. Additionally, we assess the effect of mating season and non-mating season networks in separate simulations. From these simulations, we extract information on disease persistence and critical epidemiological parameters such as the transmission rate and basic reproductive number. Compared to transmission networks, contact network-based models were found to produce improved likelihood of disease persistence, but hyper-inflated values for epidemiological parameters. Mating season networks had high seasonal rates of infection, although they were not critical to disease persistence. Our results suggest that the utility of different network types to model transmission is highly context-dependent and requires careful refinement of epidemiological parameters according to the system and networks being studied.

INTRODUCTION

Accurately modelling disease dynamics and epidemiological outcomes is critical in a world which is becoming increasingly interconnected. New opportunities for pathogen emergence, transmission and evolution have been created by rapid environmental changes and growing interactions between human populations, wildlife and domestic animals (Daszak et al. 2000; Jones et al. 2008a; Johnson et al. 2015). Predictions of how pathogens could potentially move through populations are key to our ability to reduce the threat posed by emerging infectious diseases (EIDs). The value of being able to predict, and potentially reduce, the impact of disease has implications in a suite of fields, including human health, livestock trade and biodiversity conservation (Brearley et al. 2013; Heard et al. 2013; Craft 2015). The long-term viability of wild populations, particularly endangered species, can be affected by our ability to predict and prevent the spread of pathogens (Carne et al. 2013; Scheele et al. 2014; White et al. 2014; McCallum 2016). Outbreaks can occur via spill-over (Plowright et al. 2017), or the invasion of pathogens into naïve populations, such as chytrid fungus (Stuart et al. 2004; Alemu et al. 2008; Martel et al. 2014), white nose syndrome (Blehert et al. 2009) or avian malaria (Ricklefs and Fallon 2002; Liao et al. 2017).

To understand how disease spreads through a population, there are multiple parameters that need to be estimated reliably. One of the most critical, and challenging to parameterise, is the transmission rate (β), of a given infection (McCallum et al. 2001; McCallum et al. 2017). This is commonly calculated as

$$\beta = \gamma * C \qquad \text{eq1}$$

where γ is the probability of transmission given a contact and C is the contact rate (Craft 2015). Accurate representation of the frequency of transmission-relevant contacts occurring

within a system is vital to modelling disease spread. Two key steps in making a realistic estimate of *C* are identifying contacts of transmission-relevance and quantifying their frequency (Pellis et al. 2015; White et al. 2017). The identification of transmission-relevant contacts is dependent on the host–pathogen system and its transmission mode. For diseases that require direct contact for transmission (e.g. Ebola in humans; Rizzo et al. 2016) a specific subset of contacts need to be considered, while in diseases with airborne transmission pathways (e.g. tuberculosis in the bovine/badger system; McDonald et al. 2018) close proximity to an infected individual may be considered a potential transmission event. Quantifying the frequency of potentially disease-transmitting contacts in wild populations is a challenging task. Detailed behavioural observations are required to obtain high resolution data on interactions that may result in disease transmission events (Carne et al. 2014; Fountain-Jones et al. 2017). Recent advances in telemetry, such as proximity loggers and GPS units, can also be used to obtain fine scale information on individual contact patterns, as well as temporal and spatial data. (Bull et al. 2012; Reynolds et al. 2015; Hirsch et al. 2016). This information is particularly useful to obtain contact rates for both airborne infections (which require no physical contact) and where infection is likely to spread during particular close-contact behaviours (such as denning; Blyton et al. 2014; Silk et al. 2017). Examining and incorporating these real-world contact data allows heterogeneities and non-random mixing of individuals to be accounted for, vastly improving our estimates of transmission rates and the predictive power of epidemiological models.

Social network analysis (SNA) is focused on the study of how individuals interact with one another within a system, but also how the system as a whole can change as a result of alterations in interactions at the individual level (Borgatti et al. 2009; Brockmann and Helbing 2013). Such fine-scale focus on the individual, which is imbedded in the population

network structure, is valuable in models of disease outbreak as it allows focus on precise pathways of disease movement through the network (Craft 2015; White et al. 2017). Disease modelling based on social networks has been used in management of outbreaks, or potential outbreaks, of communicable diseases in humans, such as SARS (Small et al. 2006; Brockmann and Helbing 2013), Ebola (Kiskowski 2014; Rizzo et al. 2016) and HIV (Giardina et al. 2017). The difficulty in obtaining sufficiently detailed contact histories from wildlife populations to infer disease transmission events has led to the use of two different types of networks: *contact networks*, which take into account all interactions an individual has with other members of the population and assigns a probability of disease transmission, and *transmission networks*, which make a distinction between types of contact which either actively, or potentially, result in disease transfer (Craft 2015; Chen and Lanzas 2016). In different contexts, both types of network can be incorporated into models studying disease transmission, but they would produce different estimates of important epidemiological parameters (Manlove et al. 2017) such as β and the basic reproductive number (R_0, the number of secondary cases that one case produces in a fully susceptible population).

Tasmanian devils (*Sarcophilus harrisii*) provide an opportunity to investigate the divergences in predictions of disease models based on either contact networks or potential transmission networks. Since 1996, devils have been affected by a transmissible cancer, devil facial tumour disease (DFTD; Hawkins et al. 2006). DFTD is transmitted by direct inoculation of live tumour cells when susceptible and infected individuals bite one another (Pearse & Swift 2006, Hamede et al. 2013). The disease almost exclusively affects animals of breeding age (there is no vertical transfer of DFTD from mothers to pouch young), as this is when they become involved in aggressive encounters, frequently during the mating season (Hamede et al. 2013; Hamilton et al. 2019). Devils usually die from DFTD 6 – 12 months after clinical

signs appear (Hamede et al. 2012b), although a recent study incorporating tumour growth rates demonstrated that at least 20% of devils could survive up to two years after infection (Wells et al. 2017). Given that DFTD is directly transmitted by biting, potential transmission events can be clearly identified, as the only interactions which can lead to disease transfer are those which result in bite wounds. Additionally, the use of proximity-sensing telemetry (proximity loggers) can help to determine when individuals in a population are in close contact with one another. Combining data on bite wounds from monitoring surveys and individual interactions from proximity-sensing radio-collars allows formulation of hypothetical DFTD transmission networks, as well as social contact networks. Models incorporating contact networks have been produced for DFTD previously by Hamede et al. (2012a), though these assigned a probability of infection based on close contacts and did not consider the accumulation of bite wounds within the population. Using both network types in a simulation model allows us to accurately evaluate the transmission dynamics and epidemiological outcomes of disease outbreak on susceptible populations.

Here we parameterise epidemiological models aimed at examining the spread of DFTD through a susceptible population of Tasmanian devils based on both contact networks and transmission networks. We compare model outputs in terms of persistence of the disease and estimates of the critical parameters of β and R_0 to illustrate whether predictions alter significantly or align around specific values for probability of transmission at the contact level (γ). This allows us to assess the efficacy of transmission network-based models for predicting disease spread, and whether they represent a significant improvement on the estimates provided by models parameterised with contact-based networks.

MATERIALS AND METHODS

Data collection

Interactions within an adult population of wild Tasmanian devils in the Arthur Pieman Conservation Reserve in north-western Tasmania, yet to be affected by DFTD, were recorded over a period of six months (encompassing both mating and non-mating periods) using collars fitted with proximity loggers (Sirtrack E2, Havelock North, New Zealand). Individual loggers emit a unique UHF pulse so that when two, or more, loggers are within a pre-determined distance of one another (calibrated via UHF detection range) the time, date, encounter length and unique logger number(s) are recorded and stored on the internal memory of the device. Over this period, animals were also trapped monthly and monitored for the appearance of fresh bite wounds inflicted by conspecifics. Further details of methodology and the study population can be found in Hamilton et al. (2019). Only sexually mature (two-years and older) devils were collared, as these are the animals that are involved in the transmission process of DFTD. Immature devils are unlikely to be involved in the types of interactions DFTD is transmitted during (Hamede et al. 2013), and do not reach sexual maturity until two years old in non-diseased populations close to carrying capacity (Jones et al. 2008b; Lachish et al. 2009). Additionally, there are numerous ethical and logistical constraints with collaring immature animals, particularly that they are still growing and are liable to disperse from the study population. Collars were placed only on individuals who were trapped consistently between field trips as these animals were likely to reside wholly or mostly within the study area.

Construction of base networks

Contact data obtained from the collars was filtered, eliminating "phantom contacts" of one second, and ensuring symmetry between dyads (see Prange et al. 2006, Hamede et al. 2009 and Hamilton et al, 2019 for justification and further details of methodology). Filtered contact data were first used to construct fortnightly (from January to June) contact networks based on the frequency of interactions devils had with other individuals in the population. Networks were weighted, meaning that the edges (contacts) between individuals were based on the frequency of interactions between them.

Dynamic simulation of networks

To obtain a dynamic suite of networks that encompassed the entire year, metrics for the structure of contact networks for the non-mating periods of January, May and June were used as a template to simulate contact networks for the remainder of the year (July to December). Networks from the devil's mating season (February to April) were not used in simulations of networks for the remainder of the year, as it is known from previous work that degree distribution, number of interactions (Hamede et al. 2009; Hamilton et al. 2019) and network transitivity alter significantly during this period (Hamilton et al. 2019). Networks were simulated in a weighted Exponential Random Graph Model (ERGM) framework for each fortnightly time-step, with structural components retained to produce networks that accurately reflected the interaction patterns within the wild devil population (Hunter et al. 2008; Krivitsky 2012; Silk et al. 2017a). Structural components retained were the density (proportion of connections within a network which exist, relative to the number that could possibly exist), degree distribution (proportion of nodes within the network which interact with specified numbers of other nodes), edge sex ratios (the proportion of edges between

nodes which are inter- and intra-sex) and cyclical weights (accounts for the tendency of chains between individuals to close; Morris et al. 2008) of wild devil population networks and simulating them on a fortnightly basis within the model using the R package *xergm* (Leifeld et al. 2018).

Transmission networks were constructed using a combination of proximity logger data and details of the bite wounds received by individuals. The probability of each bite wound having been inflicted by each other individual in the population was calculated based on the frequency of the wound recipient's interactions with them in the preceding fortnight, using the following equation –

$$Weight_{ij} = N_{bites} * \frac{a_{ij}}{\sum_{k=1}^{n} a_{ik}} \quad \text{eq2}$$

Where N_{bites} represents the number of bites detected, a_{ij} is the number of interactions between individual i and j, and $\sum_{k=1}^{n} a_{ik}$ is the total number of interactions between individual i and all other individuals in the population. When networks were utilised in models these probabilities were used to parameterise the likelihood that an edge (or multiple edges) formed between nodes in the network. As individuals received a different number of wounds to the number they potentially caused, networks were treated as directed i.e. each edge has an instigator (the biter) and a recipient (the bitten). The same method used to simulate contact data was used to simulate transmission networks for all time periods, including for the months of the year for which bite wound and interaction data (July to December) were not available.

Simulation model

We constructed a simulation model to predict the spread of DFTD through the naïve population on which the contact and bite wound networks were based. The model categorised individuals into one of three classes; *S* represents the class of susceptible individuals, *E* those exposed to disease but not yet infectious and *I* represents infected individuals (Figure 4.1). The exposed stage of infection (λ) was set to an average of 6 months, based on the mean distribution obtained from field estimations (McCallum et al 2009) and previous simulation studies (Hamede et al. 2012a; Wells et al. 2019). Once infected, individuals remain infected; recorded recovery rates for DFTD are close to zero (Lachish et al 2007; McCallum 2009; but see Pye et al 2016). Empirical Tasmanian devil population dynamics, based on capture-mark-recapture data from sites in north-west Tasmania, were incorporated to accurately predict the natural growth of the simulated devil population.

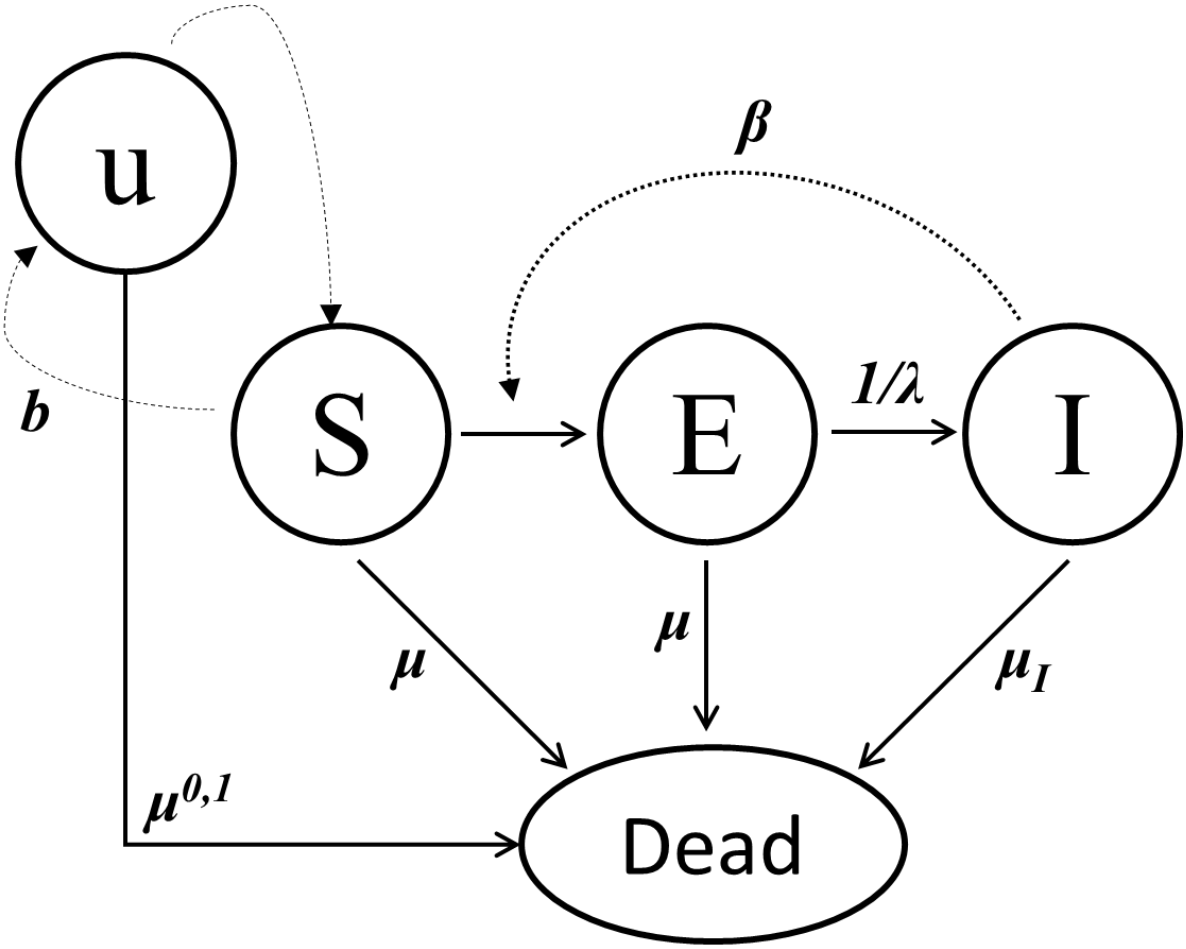

Figure 4.1 Model structure with transitions between states and input from a population model, where S = susceptible individuals; E = exposed individuals; I = infected individuals; u = population under two years old and unable to receive or transmit infection; b = birth rate; $\mu^{0,1}$ = death rate of individuals under two years old; $1/\lambda$ = latent period of infection; β = transmission rate; μ = natural death rate and μ^I = disease-induced mortality.

Models were initialised with a population of devils equivalent to that from which the interaction data were collected (12 adult females, 10 adult males, 7 non-breeding females and 10 non-breeding males). Infected status was given to one randomly selected adult in the population in the first time-step. Models were based on fortnightly time-steps to allow for increased resolution, while still retaining enough interaction data to accurately replicate

network structure. Each calendar year was thus approximated as 26 fortnights. At every time-step a series of processes were run to reflect the ongoing dynamics, patterns of contact and disease spread within the population. These processes were:

1. Age all individuals
2. Tumour growth
3. Natural mortality
4. Disease-induced mortality
5. New births
6. Rewire networks
7. Estimating new infections

1. Age all individuals

Animals in the population were aged by one fortnight at each time-step. The age of an animal in the model affects its mortality and reproductive rates (discussed in future steps). As Tasmanian devils do not reach sexual maturity and enter the breeding population until they are two years old (McCallum et al. 2009), individuals born into the population were not recruited into the SEI model, and thus able to interact with other individuals, until they reached 52 time-steps in age (the equivalent of two years).

2. Tumour growth

Once infected, tumour growth followed a logistic growth function as described by Hamede et al. (2017). This rate is based on an incremental logistic growth model that has previously

been found to fit tumour growth rates in the wild (Hamede et al. 2017; Wells et al. 2017). Tumour size was recalculated at each time-step.

3. Natural mortality

During each fortnightly time-step individual devils had a chance of exiting the population as a result of natural mortality. Natural death rate was estimated using a Heligman-Pollard-Siler model (Remund et al. 2017) accounting for increased mortality rate of juveniles, which reduces on maturity, then increases towards senescence. The natural mortality rate is based on the following function –

$$\mu(x) = A^{(x+B)^C} + D + \frac{G \cdot H^x}{1 + G \cdot H^x} \quad \text{eq3}$$

Where $\mu(x)$ represents the mortality rate at a given age, A (2.04), B (4.66) and C (-0.44) describe the juvenile mortality component, D (-0.10) describes the height of the juvenile mortality hump, and G (2.44) and H (20) incorporate the increased risk of mortality with age beyond maturity (2 years +).

A carrying capacity (100 individuals – as per Hamede et al. 2012a) was incorporated into the model and implemented by increasing mortality among 0 – 1-year old devils.

4. Disease-induced mortality

As devils generally survive between 6 and 12 months in the wild upon showing clinical symptoms of DFTD (Wells et al. 2017; Margres et al. 2018), the mortality rate of infected individuals was adjusted to reflect this. Disease-induced mortality was incorporated by lowering natural survival rates as the tumour load of an infected individual increased (Wells et al. 2017). Specifically, survival with a tumour was calculated by multiplying the base

survival rate for an individual's age class by a value for ω, adjusted based on whether the tumour load an infected animal was carrying was low (> 50–100 cm^3; ω = 0.997), medium (> 100–200 cm^3; ω = 0.975) or high (> 200 cm^3; ω = 0.958; Wells et al. 2017).

5. New births

New births occurred in an annual pulse in the seventh time step of each year (corresponding with Tasmanian devil's median birth date of 1st April; Guiler 1970; Keeley et al. 2012). Maximum number of offspring per female was four (Guiler 1970). Females are highly unlikely to breed in their first year, unless there has been severe disease-induced population decline, with breeding more likely to occur in following years (Jones et al. 2008b; Lachish et al. 2009). The number of pouch young are likely to diminish the older an animal becomes. Number of births for each female were determined from a weighted, age-specific draw according to a probability distribution based on a sample of 281 healthy female devils of age 1 to 5 (see Supplementary Materials 5.1).

6. Rewire networks

For contact network-based models, each time-step a weighted ERGM was created, modelling the likelihood of an edge between two individuals. ERGMs also included terms for devil age as a covariate and sex as a factor. Edge weights (the number of contacts between individuals) were modelled using a discrete uniform distribution, allowing values from 0 to the maximum number of contacts observed in the corresponding field data, multiplied by 1.2 (to allow for more contacts than observed in the data). A discrete uniform distribution was used primarily due to limitations in available options; use of a Poisson distribution did not capture the variation in the number of contacts. Models were checked for degeneracy and refit as required (Hunter et al. 2008; Krivitsky 2012). Validation was conducted by simulating 100

new networks based on the original starting population values and comparing density and components.

For transmission network-based models ERGMs were created as for the contact networks, but included a term representing the likelihood of an interaction between two individuals in one direction, given the presence of an interaction between two individuals in the opposite direction. Suitable ERGMs were not able to be generated for biting networks corresponding to three non-breeding fortnights; these were therefore excluded from analysis. Edge weights for transmission networks were based on a uniform distribution.

7. Estimating new infections

Each infected individual in the population was interrogated for contacts with susceptible individuals. In contact network-based models, for each contact, a binomial test was conducted based on the pre-specified transmission rate; if the result of any test was one, an infection was transmitted.

In transmission network-based models, edges in the network represent the sum of probabilities a particular interaction led to (a) bite wound(s). All edge weights (e) were totalled to produce an estimate for the total number of wounds in the time-step using a random draw from a Poisson distribution (where $\lambda = e$). These wounds were distributed proportionally to the different edges in the network, based on the simulated edge values. Transmission was subsequently determined as for contact networks (a binomial test based on the pre-specified transmission rate).

Simulations

DFTD outbreaks were simulated over a period of ten years, based on contact and transmission networks separately. Transmission probability, γ, represents the probability of an individual becoming infected given an edge with an already infected individual. To allow for direct comparison between networks types, γ was set at values of 0.1, 0.25, 0.5, 0.75 and 0.95 in a series of 500 models for each network type (Table 4.1). To test the influence of alterations to network structure during the mating and non-mating seasons, a further series of 500 models were run at each value of γ incorporating: 1) only mating season networks, and 2) only non-mating season networks. The missing networks in each series were replaced with empty networks, where no opportunities for transmission occurred.

Parameter	Symbol	Value
N^o adult devils	N	22
N^o 0 – 1 y.o. devils (non-breeding)	N_u	17
Sex ratio	s	50:50
Annual recruitment rate	b	0 – 4 / female
Natural mortality rate	μ	Via Heligman-Pollard-Siler model
Carrying capacity	K	100
Transmissibility	γ	0.1; 0.25; 0.5; 0.75; 0.95
Latent period	λ	13 fortnights
Disease induced mortality	μ_I	0.997 to 0.958 depending on tumour load
Rewiring interval		1 fortnight
Recruitment interval		26 fortnights
Recruitment time		Fortnight 7 annually

Table 4.1 Parameters and terms used in models simulating outbreaks of DFTD in a susceptible Tasmanian devil population.

Once all models had run, transmission rate, β, was calculated for each time-step by multiplying the fixed value of γ (transmission probability) for the run by the number of contacts (or bite wounds) occurring in that time-step (C). A basic time-step value for R_0 (the number of new DFTD cases arising from a primary case in a fully susceptible population) was calculated using the following equation –

$$R_0 = \frac{I_N}{I} \qquad \text{eq4}$$

Where I is the number of infected individuals in the population and I_N is the number of new DFTD cases arising in that time-step. Only instances where DFTD was still present within the population were used to calculate the values for both β and R_0 (i.e. when DFTD was extinct in the population, zeroes obtained for both these parameters were excluded from calculations of the mean).

RESULTS

Epidemic outcomes

In models using contact networks, the probability of DFTD persisting after a period of ten years ranged from 0.74 (γ = 0.1) to 0.91 (γ = 0.95; see Figure 4.2). Persistence values were not substantially reduced when mating season networks were excluded from the model (0.65 at γ = 0.1 to 0.91 at γ = 0.95; Figure 4.2). However, when only mating season networks were incorporated, probability of persistence reduced substantially – from as low as 0.01 (γ = 0.1) to a maximum persistence probability of 0.46 (γ = 0.95; Figure 4.2). When disease persisted in the populations modelled on full contact networks, prevalence in the adult population levelled off at a mean value of 0.69 (± 0.004) at the highest value of γ (0.95; Figure 4.3). Mean prevalence reduced to 0.41 (± 0.004) at the lowest value of γ modelled. Mean

prevalence in the populations modelled excluding mating season networks was significantly lower at all values of γ (0.34 ± 0.004 at γ = 0.1; 0.70 ± 0.004 at γ = 0.95; Figure 4.3). When only mating season networks were considered, adult prevalence at γ = 0.1 declined to 0.01 (± 0.0004), climbing to 0.22 (± 0.003) at a value of γ = 0.95 (Figure 4.3).

In models run using transmission networks the probability of DFTD persisting after ten years declined dramatically for all values of γ. For values of γ below 0.5, DFTD was unable to persist within the population when any combination of networks was incorporated (Figure 4.2). When only mating season transmission networks were used, DFTD was unable to persist in the population at any value of γ. When all transmission networks were incorporated, persistence rate ranged from 0.03 at γ = 0.5 to 0.28 at γ = 0.95 (Figure 4.2). The upper limit of this range was somewhat lower when mating season networks were excluded (0.03 at γ = 0.5, to 0.22 at γ = 0.95; Figure 4.2). DFTD prevalence showed a tendency to decline over time when modelled on transmission networks. At the highest value for γ (0.95) average annual prevalence peaked at 0.16 (± 0.008) in the second year and had declined to 0.08 (± 0.006) by the tenth (Figure 4.3). This pattern was replicated in the models excluding mating season transmission networks, though with lower mean values for prevalence (Figure 4.3).

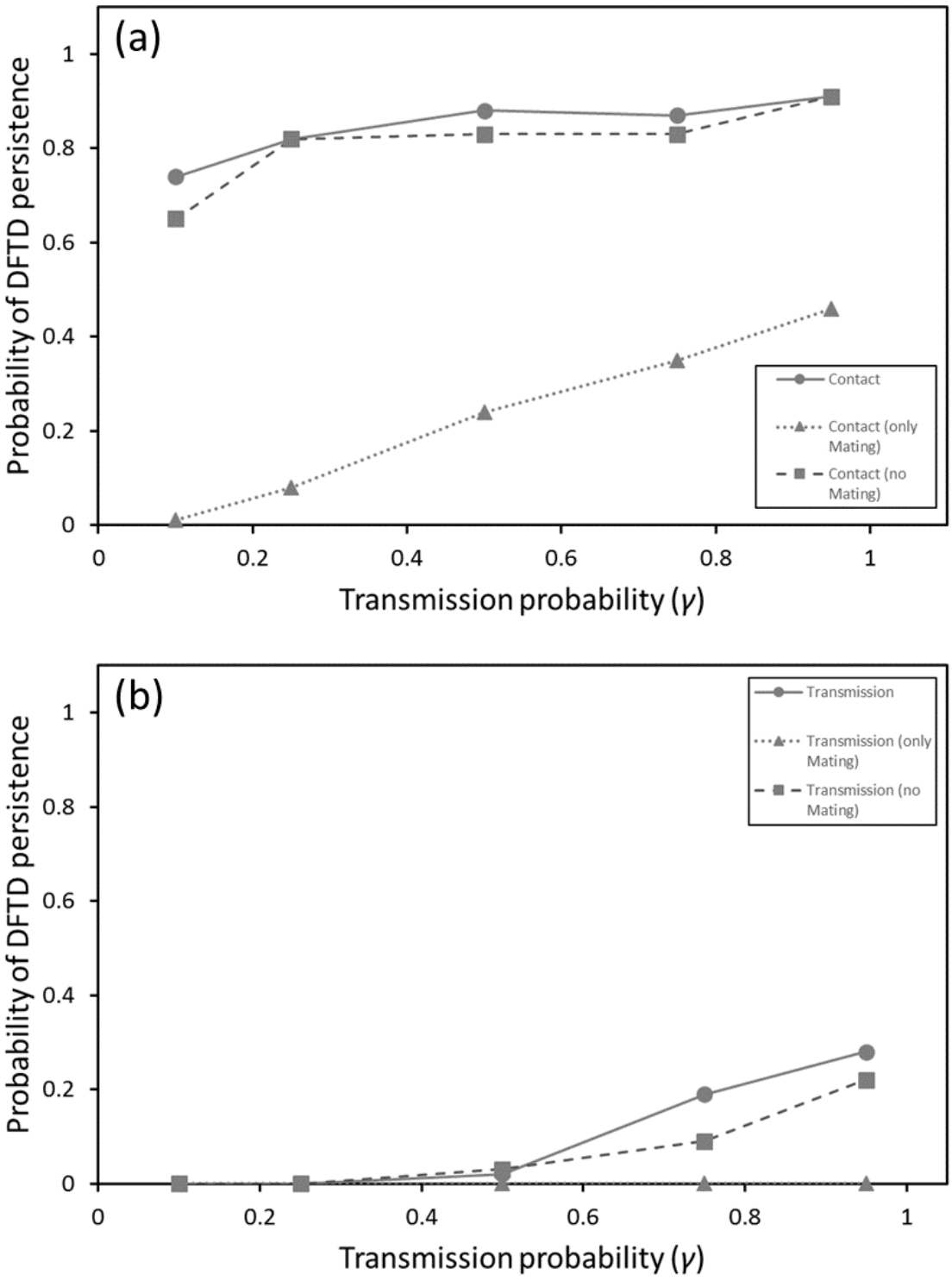

Figure 4.2 Probability of DFTD persistence in 500 runs of simulation models based on varying values for transmission probability (γ) and using either (a) contact, or (b) transmission networks.

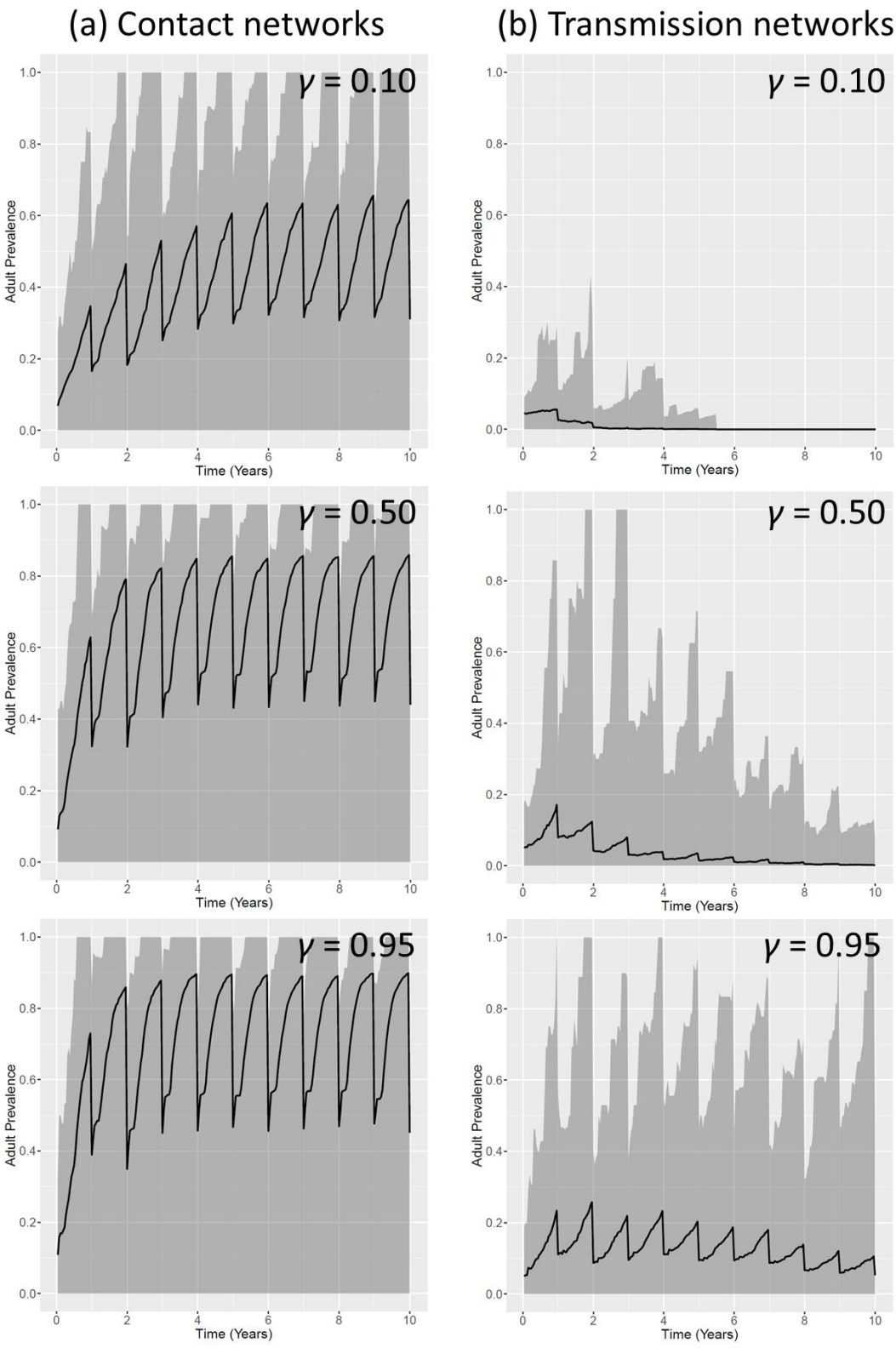

Figure 4.3 Mean adult prevalence of DFTD (with full range of values in dark grey) across 500 simulations of contact and transmission networks at varying values of γ (transmission probability).

Estimates of transmission rate (β)

Estimates for β derived using contact networks were several orders of magnitude higher than those derived using transmission networks. Full contact network estimates of β peaked at 281.93 (± 26.03) for the highest value of γ (0.95), compared to 2.06 (± 0.12) in the full transmission networks (Figure 4.4). The lowest value of β predicted by full contact networks (at $\gamma = 0.1$) was 14.43 (± 1.37), contrasting with 0.08 (± 0.01) from the full transmission networks (see Figure 4.4). In both contact and transmission networks, estimates of β did not differ significantly when mating season networks were excluded. However, when models were run using only mating season networks estimates of β were significantly reduced (Figure 4.4).

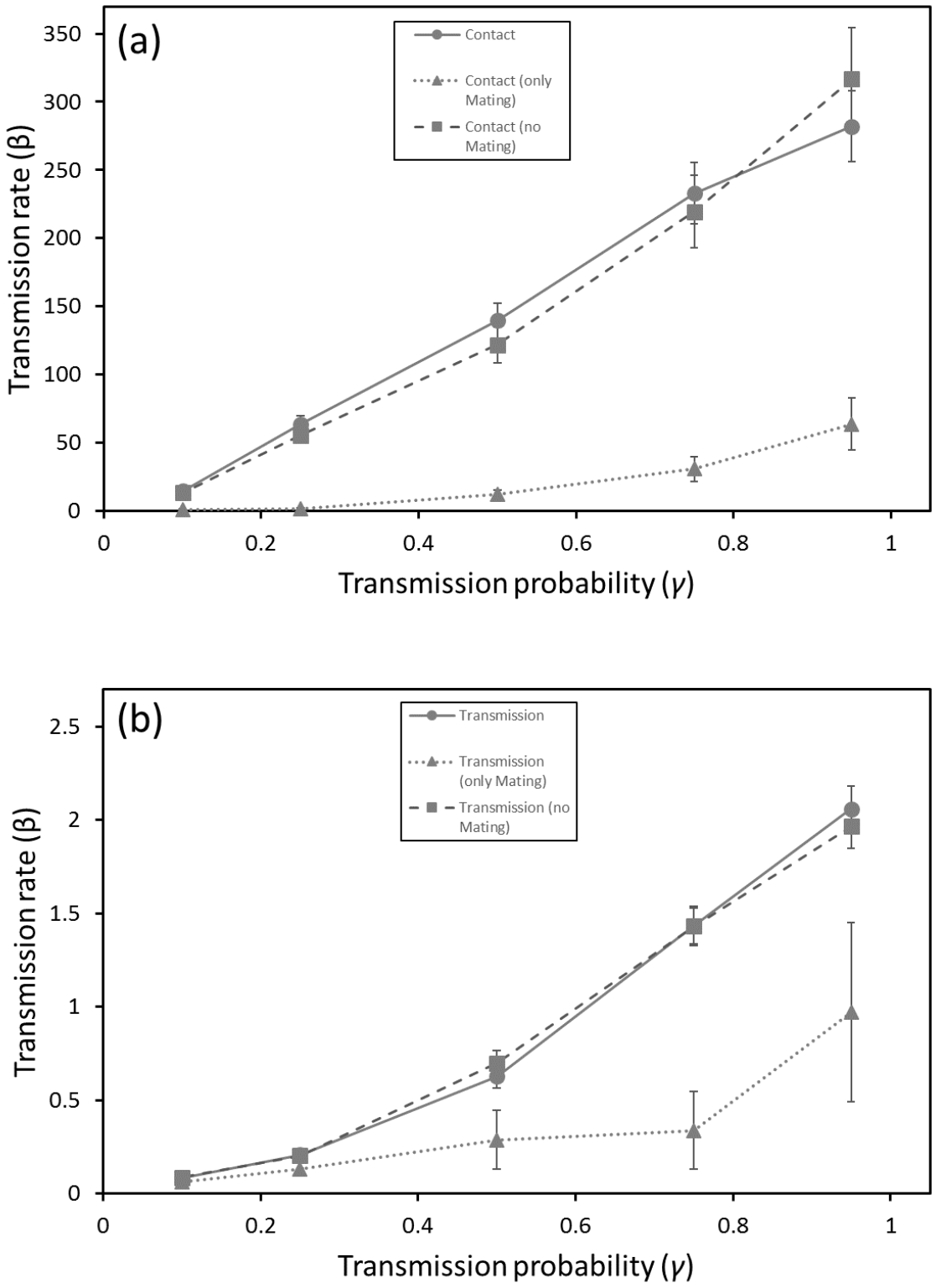

Figure 4.4 Mean estimates of fortnightly transmission rate (β) derived from 500 simulations of (a) contact and (b) transmission networks at increasing values of γ (transmission probability). Error bars represent 95% confidence intervals.

Estimates of the basic reproductive number (R_0)

Contact network-parameterised models produced estimates for R_0 which only exceeded the persistence threshold (> 1) when values for γ were 0.5 or greater (Figure 4.5). Patterns for full networks and those excluding mating season networks were identical, increasing as transmission probability increased. Models using contact networks including only the mating season showed the opposite trend, declining as the value of γ increased (Figure 4.5).

Transmission network estimates for R_0 exceeded the persistence threshold only in full contact network models where γ was at its lowest value (0.1; Figure 4.5). Patterns for models run using full networks, mating season networks only and excluding mating season networks followed similar trends, remaining just below 1 for values of γ of 0.25 or greater (Figure 4.5).

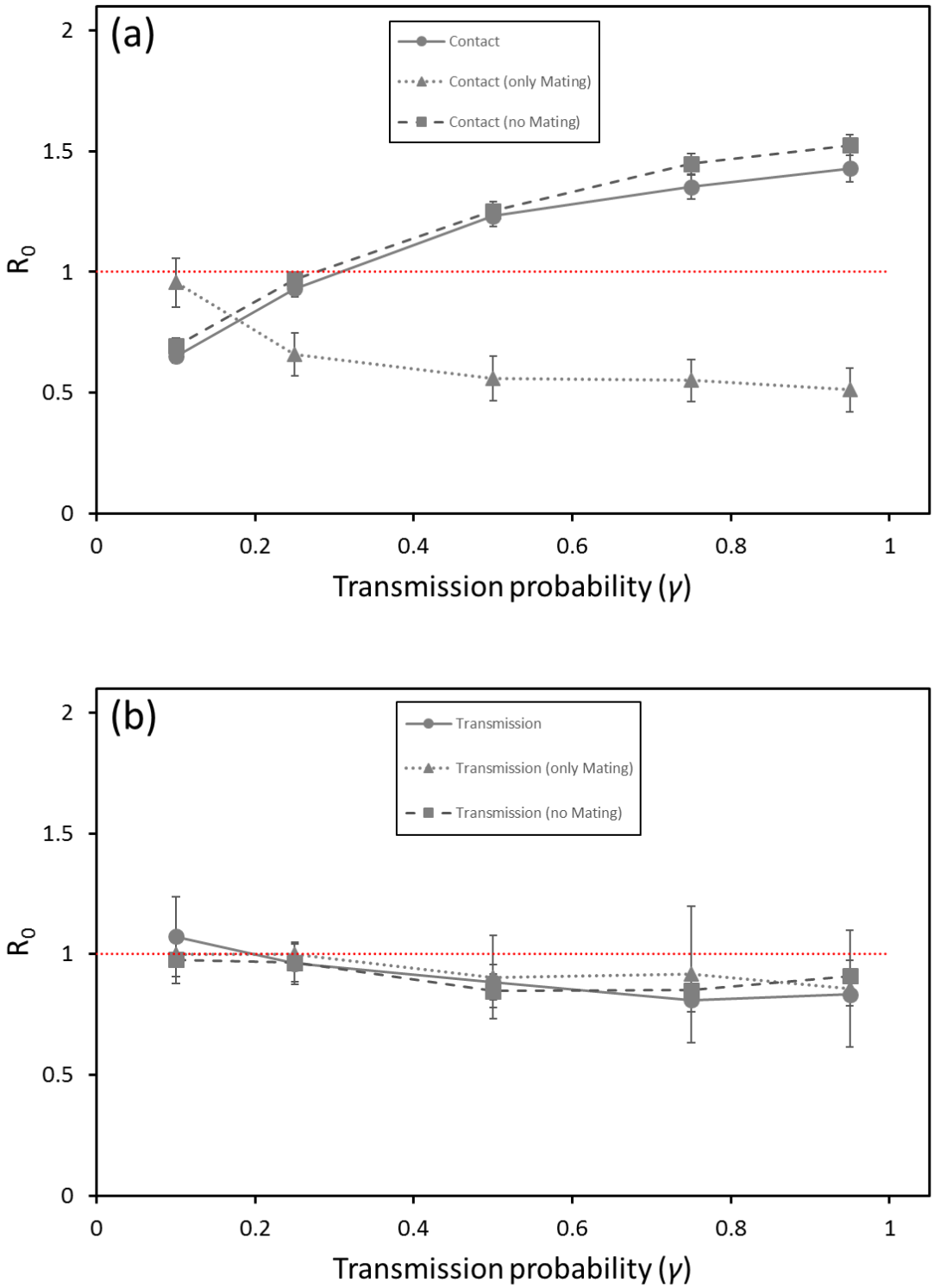

Figure 4.5 Mean estimates of fortnightly R_0 (basic reproductive number) derived from 500 simulations of (a) contact and (b) transmission networks at increasing values of γ (transmission probability). Error bars represent 95% confidence intervals. The dotted red line represents the R_0 threshold beyond which infection can persist.

DISCUSSION

Predictions made by simulations on contact- and transmission-based networks are expected to vary in terms of outbreak outcomes and epidemiological parameters (Craft 2015). When such networks are applied to the Tasmanian devil-DFTD system, contact networks predict sustained, extensive epidemics. Conversely, transmission networks project low likelihood of infection persistence at reduced prevalence, even at extremely high values for probability of infection. In both network types, dense mating season networks are observed to be of lower importance to persistence than consistent rates of infection through the year via less dense networks. Estimates of transmission rate are hyperinflated in contact networks compared to transmission networks. R_0 estimates are sufficient to sustain infection in contact networks for higher values of transmission probability, while remaining relatively consistent at around, but almost exclusively below, the threshold in transmission networks. Together these results illustrate the contexts in which different networks may be useful, and the importance of appropriate epidemiological parameter values to fit divergent network types and host-pathogen systems.

Transmission networks based on bite wound incidences indicated that DFTD is unlikely to persist in a population for greater than ten years. This pattern is not observed in the wild, with multiple local populations of Tasmanian devils having maintained high prevalence of the disease for over a decade (Lazenby et al. 2018). Contact networks were more likely to predict long-term persistence of the disease, with prevalence in the adult population of greater than 40% even at low values for transmission probability. This prediction is more consistent with long-term population trends of DFTD, which ranges in prevalence from < 10% to > 50% of monitored populations (note that these figures include juveniles) of Tasmanian devils

(Lazenby et al. 2018). Looking beyond ten years, Wells et al. (2019) predicted that, if current transmission dynamics persist, DFTD has a 57% chance of fading out in Tasmanian devil populations within 100 years. Such a pattern is supportive of the declining prevalence trajectory predicted using transmission networks, rather than the state of equilibrium attained using contact networks.

There are three aspects which may be limiting the potential of our transmission-based models to predict long-term DFTD trends. Firstly, once DFTD becomes established within a population, with subsequent population declines and age structure becoming biased towards young individuals, females begin to breed during their first year of life (Jones et al. 2008b). This pattern of precocial breeding increases the proportion of susceptible animals in the long-term. This is a pattern we were unable to replicate here, due to the difficulty of obtaining data on juvenile contact rates and how they change with time since disease outbreak. Secondly, bite wound data collected from a healthy Tasmanian devil population may underestimate the number of wounds occurring in a DFTD-affected population. Large facial tumours present clear targets for biting on infected devils, so may incur more bite wounds than a healthy devil involved in similar interactions. Bite wounds occurring on tumours themselves are difficult to quantify in the wild, as they are indistinguishable from ulcerations. The third limitation is the spatial context of the epidemic, accounting for the possibility of DFTD entering the affected population from adjacent areas. Patterns of reinfection of local populations, with the disease emerging locally then being replaced by genetically distinct lineages, have been observed in the wild (Hamede et al. 2015; Siska et al. 2018). This cycle is likely to allow DFTD to remain prevalent in local populations, even as infected residents die off regularly. Incorporation of such patterns may increase the reliability of predictions, though it would require data on tumour lineages, which was not possible in this case as the study population was DFTD-free.

In all likelihood, dynamics of populations and transmission will alter through time, meaning the networks used here are better suited to predicting dynamics in the initial years of outbreak, rather than in the longer term.

Predictions of transmission rate, β, varied greatly between contact and transmission network-based models. β is effectively the number of contacts in a given time period that result in an infection transmitting to a susceptible individual. The predictions for this parameter using contact networks produced unrealistically high values. Conversely, estimates for β using transmission networks produced lower values than is sufficient to maintain population infection in the long-term. In this system, contact-based models over-inflate the influence of benign contacts, particularly at high values for transmission probability. In reality, the proportion of overall contacts which result in bite wounds is 1% (Hamilton et al. 2019); this would mean a transmission probability of < 0.01 is required to use contact networks to accurately portray likelihood of transmission in the wild. However, this would not represent seasonal variations in likelihood of injury (Hamede et al. 2013; Hamilton et al. 2019), making a seasonally shifting value for transmission probability a more realistic way to model temporal dynamics in contact networks. A shifting value would reflect periods of time within contact networks when contact rate is extremely high, but the likelihood of receiving a wound is low (Hamilton et al. 2019). In the contact networks modelled here, these periods are likely to retain high values for β, while they reduce dramatically in networks considering only bite wounds. With regard to transmission network-based models, the number of bite wounds within the population cumulatively does not appear to be enough to maintain a high value of β over an extended period, even when transmission probability is close to 1. Population numbers do not crash in the incidences where the disease fades out, indicating that failure to persist is not the result of a lack of hosts. Instead, fade out could be attributed to infected

hosts dying before they have the opportunity to pass on infection. Bite wound incidences are rare enough to make the likelihood of multiple infected animals being involved in them regularly relatively low. Number of bite wounds is sufficient to initiate epidemics initially, but increased bite wound frequency in some individuals post-infection may be required to maintain prevalence over time (as is the case with rabies, for example; Holmala and Kauhala 2006). This is another factor that could be accounted for by large tumours being the target of increased numbers of bites, as mentioned above. Optimum utility of these networks is likely in predicting initial disease dynamics, rather than long-term transmission trends.

We parameterised transmission probability up to an extremely high value in both sets of models to allow for direct comparison. In reality it is clear that, while high transmission probability is likely given a bite wound, it is not realistic when considering all contacts occurring within a population. A very high proportion of contacts occurring between devils are benign (Hamilton et al. 2019), and the result of close-range activities that present less opportunity for transmission. These include individuals denning together in the non-mating season (Hamilton et al. 2019) and side-by-side consumption at carcasses (an activity which rarely translates to injury; Hamede et al. 2008). The appropriate use of contact networks is likely to be contextual. For example, high transmission probabilities given close proximity are likely in the case of airborne pathogens, such as pneumonia (Manlove et al. 2017) or SARS (Pourbohloul et al. 2005). Alternatively, contact networks filtered by the context of interactions can be extremely accurate predictors of transmission pathways (Blyton et al. 2014). In Tasmanian devils, the use of bite wound-based transmission networks more accurately portrays disease-transfer opportunities occurring during contacts, necessitating the use of high values of transmission probability.

Predictions of R_0 between network types display similar overall patterns to those for β, with those made by transmission networks proving insufficient to maintain DFTD persistence. Of interest is the additional observation that, for all transmission networks and contact networks incorporating only mating season data, R_0 is slightly higher at low transmission probabilities. This pattern may be explained by the requirement for R_0 to be maintained at a higher level for DFTD to persist in instances where the likelihood of infection is low. The value for R_0 for DFTD has been estimated previously to lie between 1 and 3 in simulated contact network models (Hamede et al. 2012a) and between 1.3 and 9.6 from field estimates. These values reflect only the estimates made by contact networks at values of transmission probability of 0.5 and above, which also produce unrealistically high values for β. The comparatively lower values for R_0 over time predicted by the contact networks, even in cases where transmission probability is high, may be a reflection of infections occurring in bursts. High transmission probabilities, coupled with high numbers of opportunities for transmission, in contact networks results in all susceptible individuals within a population becoming infected very quickly. As a result, R_0 will be temporally elevated in the time periods where all susceptible individuals become infected, but then reduce to zero until more susceptibles are recruited into the population. Such a pattern is not reflective of dynamics in the wild, with new infections observed to occur throughout the year, rather than in sustained seasonal bursts (Lachish et al. 2007; McCallum et al. 2009). Lack of infection bursts in wild populations may be partially attributable to the distributed delay in latent period of DFTD. A more variable period prior to becoming infectious would reduce the likelihood of seasonal clusters of infections occurring, potentially altering estimates of R_0.

The importance of mating season networks was less than what may have been predicted, particularly given their previously highlighted potential importance in disease transmission

(Hamede et al. 2009; Hamede et al. 2013; Hamilton et al. 2019). Models based solely on mating season networks were insufficient to maintain long-term DFTD infection, while also producing much lower estimates for β using both network types. Such patterns would indicate that, while mating season interactions are likely to be important in seasonal transmission rates, maintenance of infection within populations is driven by transmission opportunities that occur year-round, both during and outside the mating season. Aggressive contacts do still occur during the non-mating period, albeit at a vastly reduced frequency (Hamilton et al. 2019). Infections occurring during this period are likely important in ensuring that there are still infected individuals in the population by the next mating season. At the subsequent mating season, increased transmission will occur, as male and female devils become involved in aggressive mating interactions. While mating season interactions facilitate transmission, long-term infection at the population level is dependent on ongoing transmission events occurring throughout the year.

Contact and transmission networks are useful to our understanding of epidemiology, though the contexts in which each is used must be carefully considered and tailored to the host-pathogen system. Here we have made the first attempt to assess the performance of simulation models for DFTD based on projected transmission networks. In practice, they perform sub-optimally at long-term projection, but may be of utility in predicting initial stages of DFTD epidemics. Long-term predictions using either contact or transmission-based networks is challenging due to the difficulty of accurately reflecting the complex spatial and temporal changes that occur in Tasmanian devil populations affected by DFTD. Long-term DFTD dynamics are better predicted by using Bayesian-based approaches incorporating known population dynamics of infected populations through time (Wells et al. 2019). Studies comparing the performance of contact and transmission network-based models are rare,

however. We have illustrated the importance of fine-tuning epidemiological parameters to suit the systems and networks being modelled. Further comparison of both network types is important to our understanding of the contexts in which different epidemiological models may be informative. A key facet of this is whether such high-resolution information as that provided by transmission-based networks is strictly necessary to provide accurate predictions of disease transmission processes, from initial stages of epidemic outbreak to long-term dynamics of infection.

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SUPPLEMENTARY MATERIALS – CHAPTER 5

Supplementary Materials 5.1 *Probability distribution of birth rates*

	Pouch Young				
Age	**0**	**1**	**2**	**3**	**4**
0	1	0	0	0	0
1	0.969072	0	0	0	0.030928
2	0.196429	0.053571	0.107143	0.196429	0.446429
3	0.066667	0.111111	0.222222	0.4	0.2
4	0.277778	0.222222	0.222222	0.277778	0
5	0.777778	0	0	0.111111	0.111111

Table S5.1 Probability distribution of the birth rate of Tasmanian devils of different ages based on the number of pouch young carried by sample of 281 healthy females caught in north-west Tasmania between 2015 and 2018.

Chapter 5

Cancer and sickness behaviour: tumour progression affects interaction patterns and social network structure in wild Tasmanian devils

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ABSTRACT

Cancer can have demonstrable impacts on behaviour, particularly in the latter stages of infection. However, studying behavioural influences of cancer is challenging in wild animals due to the difficulty of early diagnoses. Tasmanian devils (*Sarcophilus harrisii*) are affected by a transmissible cancer, devil facial tumour disease (DFTD), in which tumours are externally visible as they progress. We quantify the impacts of cancer progression on the behaviour of a wild population of devils by assessing how interaction patterns within their social network alter on infection and with increasing tumour load. We also examine whether devil's interaction patterns influence their probability of exhibiting clinical signs of DFTD in the short-term. DFTD negatively influences devil's likelihood of interaction within their network, an effect which increases with increasing tumour load. There was no demonstrable link between devil's position within their social network and likelihood of displaying clinical DFTD symptoms within six-months. Our results contribute towards our understanding of behavioural feedbacks of cancer and how they may affect transmission, and population, dynamics in this and other systems.

INTRODUCTION

Behavioural interactions are influenced by a suite of factors, both proximate and ultimate (Telfer et al. 2010; Gallana et al. 2013; Lowry et al. 2013). Disease can be a strong driver of interaction tendencies in both wildlife and human populations (Kappeler et al. 2015). The extent of influence depends on multiple variables, including social system of the host, environmental stressors, pathogen virulence and the long-term consequences of infection (Hart 1988; Adelman et al. 2010; Ghai et al. 2015; Bohn et al. 2016). Alterations to behaviour can be driven by gradual physiological changes in the host (Aubert 1999), expected to be contingent on infection stage. As a result, there is often a threshold at which behavioural changes begin to occur or increase in intensity (Szyszka and Kyriazakis 2013). Individual changes in behaviour influence interaction dynamics and so, ultimately, infection-induced alterations in behaviour have potential impacts not only on the host, but on transmission dynamics and epidemiology.

Behavioural responses to infection tend to be the result of two disparate, but potentially interacting, factors – avoidance of disease carriers by healthy individuals and disease-induced changes in behaviour of infected individuals. The first is caused by active avoidance of diseased individuals (Behringer et al. 2006), driven by selective pressure on healthy individuals to avoid infection. The tendency for avoidance to occur depends on the relative cost of infection, as well as the social system of the host and the context of interactions (Fairbanks et al. 2014). The effects of disease itself induces behavioural changes in the host. Infected animals have to trade-off the energy allocated to the different components of fitness: fighting infection to survive and reproduce to contribute to the multi-generational gene pool (Vittecoq et al. 2015). The suite of behavioural responses to infection are collectively termed

"sickness behaviours" and tend to be associated with energy conservation (Hart 1988; Hart and Hart 2019). In some cases, the development of infection may alter behaviour progressively, as condition of the animal worsens and demands on the immune system increase. Over time, infection can drive animals into social isolation, to avoid potentially costly competition with conspecifics or to conserve energy (Johnson 2002; Ghai et al. 2015). Alternatively, there may be fitness benefits to aggregating, which can help reduce the cost of an infection (Dawson et al. 2018). The effects of avoidance and sickness behaviours can be difficult to disentangle in populations of wild animals. For example, Weber et al. (2013) found that European badgers (*Meles meles*) infected with bovine tuberculosis (*Mycobacterium bovis*) were socially isolated from their own social groups, but it was unclear whether this was the result of avoidance by healthy individuals or of infected individuals isolating themselves. Overall, the effects and progression of sickness behaviour remain relatively poorly studied in free-living wildlife populations.

Studying the effects of disease-induced behavioural changes of individuals requires detailed and time-step knowledge of disease status and interaction patterns. This has been achieved in some group-living species, notably primates, mongooses and mice (Ghai et al. 2015; Flint et al. 2016; Lopes et al. 2016). However, detailed study is particularly challenging in non-gregarious species where interactions are less common, but in which those infrequent interactions may be particularly important for pathogen transmission. A further complication is the difficulty of timely assessment of clinical diagnosis of infection in wild animals (Artois et al. 2009). Many diseases can induce behavioural or physiological changes without the host displaying clinical symptoms, such as Ross River virus (Claflin and Webb 2015). Other diseases with high morbidity, such as cancer, are particularly difficult to diagnose in wild populations (Vittecoq et al. 2015; Ujvari et al. 2016; Ujvari et al. 2019). Animals affected by

cancer are generally not diagnosable until tumours are sufficiently large to be visible externally, and they can often die without ever showing clinical symptoms (Thomas et al. 2017). Studying the behavioural effects of oncogenic processes in wild populations is both ecologically and epidemiologically relevant across a broad range of taxa, as cancer is a highly virulent and ubiquitous disease present in all multicellular organisms (Leroi et al. 2003). Studying behavioural changes as a result of cancer in wildlife requires a system in which 1) individuals with cancer display clinical signs that are clearly diagnosable at an early stage of development, and 2) the interactions of individuals in a population can be monitored during disease progression.

Here, we follow the progression of cancer-induced behavioural changes in a solitary animal, the Tasmanian devil (*Sarcophilus harrisii*), caused by a transmissible cancer, devil facial tumour disease (DFTD; Woods et al. 2018). DFTD is a clonal cancer cell-line (Pearse and Swift 2006) transmitted between hosts when they bite one another, predominantly in and around the oral cavity (Hamede et al. 2013). Transmission is driven by the social and aggressive behaviours of the species, resulting in bite wounds (Hamede et al. 2013; Hamilton et al. 2019). Once infected, tumours develop around the head and mouth of the host, resulting in death after 6 – 12 months in most cases (Hamede et al. 2012; though see Wells et al. 2017). The disease has a severe impact on the health of infected individuals, particularly in the latter stages of infection when animals are often severely immunocompromised, in poor condition and likely to be uncompetitive in resource acquisition (Ruiz-Aravena et al. 2018). As tumour load increases, animals can have difficulty feeding, due to tumours displacing teeth or obstructing the palette and throat. This is likely to impact their energy intake, and progressively reduce their ability to compete with conspecifics for further resources. In addition, the metabolic cost of DFTD on the host grows as tumours become larger, further

increasing the need to conserve energy (Ruiz-Aravena et al. 2018). As a result, increasing tumour load is expected to influence interactions between the host and other individuals, with consequences for further transmission of the pathogen.

In this study, we use proximity logger telemetry to generate contact networks and investigate interactions within a population of Tasmanian devils recently infected with DFTD. Over a six-month period, we closely monitored both interactions and disease status of the adult population to test the effects of DFTD and tumour load on contact patterns. We use temporal exponential random graph models (TERGMs), which utilise social network theory to model an individual's probability of interacting with others in the population over time, while also accounting for changes in disease status. We use a series of network autocorrelation models (NAMs) to look for links between an animal's network position and its probability of switching to a diseased state over the six-month period. This allows an evaluation of how cancer progression might alter social behaviour over a temporal scale, in addition to how network position may influence infection probability at the individual level.

MATERIALS AND METHODS

Proximity loggers

Proximity loggers fitted to adjustable collars (Sirtrack E2, Havelock North, New Zealand) were used to collect data on interactions between devils. Individual collars emit a unique UHF pulse, such that when two, or more, units are proximal, details of the interaction are recorded on the device's internal memory. Collars were calibrated to detect and log one another at a distance of 30cm or less – a biologically meaningful distance at which devils could conceivably bite one another. Proximity loggers were set up and calibrated to be consistent with previous research on Tasmanian devil interactions (see Hamede et al. 2009 and Hamilton et al. 2019 for further details of proximity logger calibration and data handling).

Field site and data collection

The study was conducted in a population of Tasmanian devils near Smithton in north-western Tasmania (-40.980 E, 145.263 S). Tasmanian devils were caught for collaring by setting 40 traps over a 25km^2 area for a period of one month. Traps were custom built of 300 mm polypipe and baited with various meats (predominantly lamb and macropod). The population had been surveyed for 6 months prior to commencement of collaring, allowing identification of resident individuals in the core study area. All known sexually mature individuals (two years and older) were caught and collared in January 2017 (12 females, 10 males). Proximity loggers were activated and collecting data on individual's interactions from January until the end of June. This period covers both mating (February to April) and non-mating periods (May to June), when devil interaction rates differ significantly (Hamede et al. 2009; Hamilton

et al. 2019). Timing of the mating season was clear from extended intersex interactions recorded by the proximity loggers during this period, but was also confirmed by backdating birth dates of pouch young based on their developmental stage (see Hesterman et al. 2008 and Hamede et al. 2009).

Collared devils were re-trapped on a monthly basis throughout the study period in order to monitor their disease status, record bite wounds and to assess collar fit. Upon capture, devils were thoroughly examined for the appearance of facial tumours. For all tumours, the length, width and depth were recorded to 0.1mm using callipers. These measurements were used to calculate the volume of each tumour according to the following formula -

$$Volume = \left(\frac{4}{3} * \pi\right) * \frac{Length}{2} * \frac{Width}{2} * \frac{Depth}{2}$$

Multiple tumours on each individual devil for each capture were pooled to obtain a value of tumour load per individual. Tumour load on each individual at each timestep was categorised into four levels (as per Wells et al. 2017); (1) 0.0001 – 50 cm^3, (2) > 50 – 100 cm^3, (3) > 100 – 200 cm^3 and (4) > 200 cm^3. Devils were also checked thoroughly for the appearance of new wounds (see Hamilton et al. 2019 for full details and rationale of wound checking procedure).

Network construction

Contact networks were constructed using two temporal separations. The first set of networks (used in the TERGM analysis detailed below) were formulated using filtered contacts for twelve fortnightly periods running from the start of the study (the point at which all adult animals in the population had been collared – 19th January). The second set of networks (used

in the NAM analysis detailed below) were separated into mating (16th February - 26th April) and non-mating (19th January - 15th February and 27th April – 5th July) seasons. In both sets of networks, individuals are represented as nodes linked by observed contacts – lines (edges) between nodes are weighted by the frequency of contacts. All networks were produced using the *igraph* package in R v3.2.5 (R Core Team 2018).

Within each fortnightly network, we calculated five node-level network metrics using *igraph*. All provide an indication of an individual's position and interactive potential within the network – total number of interactions, weighted degree (the number of other individuals associated with), betweenness centrality (the number of shortest paths flowing through an individual), closeness centrality (sum of all shortest paths flowing through an individual) and clustering coefficient (measure of how many of an individual's connections are also connected). For each metric within each time-step, we used a node-permuted general linear model to test for differences between healthy and DFTD-infected individuals. To account for the non-independence inherent in network analysis (Croft et al. 2011; Farine and Whitehead 2015), these were compared to 10,000 randomised networks that had their nodes shuffled by disease status

Temporal Exponential Random Graph Models (TERGMs)

Temporal exponential random graph models (TERGMs) were used to investigate whether devil's interaction patterns within a contact network differ as a result of infection status, tumour load or number of wounds accrued (a proxy of infection risk – see Hamede et al. 2013). TERGMs can be used to examine network structure through time, allowing evaluation

of the effect of DFTD on interaction patterns. TERGMs were run using the package *btergm* (Leifeld and Cranmer 2015). All analyses were conducted in R 3.5.2 (R Core Team 2018).

Separate TERGMs were independently fitted to examine the effects of DFTD status, tumour load and number of wounds accrued on edge formation within binary fortnightly contact networks. These models were further subdivided into mating and non-mating season to account for known seasonal variability in Tasmanian devil interactions (Hamede et al. 2009; Hamilton et al. 2019). Each model included the following terms; *edges* – similar to the intercept term in a General Linear Model, this gives the probability of edges forming in a network relative to a random network (Silk et al. 2017); *memory* – models if interactions remain consistent over time; *nodefactor (Sex)* – models sex-based variations in interactions; *nodemix (Sex)* – accounts for any tendency for sexes to interact preferentially. The final *nodefactor/cov()* in each model was aimed at examining the tendency of interactions to vary based on the key variables of DFTD status (binomial factorial), tumour load (continuous numerical covariate) or number of wounds (discrete numerical covariate). Each model used maximum likelihood estimation and was bootstrapped 10,000 times to obtain confidence intervals.

Network Autocorrelation Models (NAMs)

To test whether a devil's interaction patterns within a season affected their likelihood of having acquired DFTD by season-end, we ran network autocorrelation models using the package *tnam*, within the *xergm* suite (Leifeld et al. 2018). Models were fitted using infection status at the end of the season as a binary response (using a binomial family model) and were run on weighted networks for the mating and non-mating season respectively. Each model

fitted sex as a fixed effect, with number of wounds accrued during the season included as a covariate. As previously mentioned, the number of wounds accrued represent potential transmission events. We hypothesised that increased biting events that result in wounds, increased the likelihood of developing DFTD. Terms for the subset of node-level social network metrics examined during network construction (weighted degree, betweenness centrality, closeness centrality and clustering coefficient) were also fitted, to examine whether any aspect of an individual's role within the network influenced its probability of developing DFTD in the short term. No metric examined significantly correlated with any other. All network terms were centred, and the non-independence of connected individuals in the network was accounted for using a *weightlag* term in the model.

RESULTS

Contact networks

The total number of interactions recorded over the six-month period was 8,504 (7,273 in the mating season, 1,231 in the non-mating season). At the beginning of the study, three individuals had clinical symptoms of DFTD infection, while a further seven individuals began displaying clinical symptoms during the following six months; the remaining twelve devils remained healthy throughout the study period (see Figure 5.1). Network density was significantly higher in fortnightly mating season contact networks (0.14 ±0.02) than non-mating season contact networks (0.09 ±0.02).

Interaction frequency differed significantly between healthy and DFTD infected individuals for the entirety of the mating season (Figure 5.2a; node-permuted GLMs; f3, $P = 0.001$; f4, P

= < 0.00001; f5, *P* = 0.015; f6, *P* = < 0.00001; f7, *P* = < 0.00001) and for two fortnightly periods in the non-mating season (Figure 5.2a; f9, *P* = 0.006; f10, *P* = < 0.0001). Degree was significantly lower in DFTD-infected individuals during the first three fortnightly periods of the mating season (Figure 5.2b; f3, *P* = 0.033; f4, *P* = 0.045; f3, *P* = 0.012). Betweenness was significantly lower in DFTD-infected animals for the first two non-mating fortnightly periods in the study (Figure 5.2c; f1, *P* = < 0.00001; f2, *P* = < 0.00001) and three fortnights within the mating season (Figure 5.2c; f3, *P* = < 0.00001; f5, *P* = < 0.00001; f6, *P* = < 0.00001). Closeness was only found to be significantly divergent (higher in healthy devils) for one fortnight during the mating season (Figure 5.2d; f1, *P* = 0.029), while clustering coefficient was not significantly different during any fortnightly period of the study (Figure 5.2e).

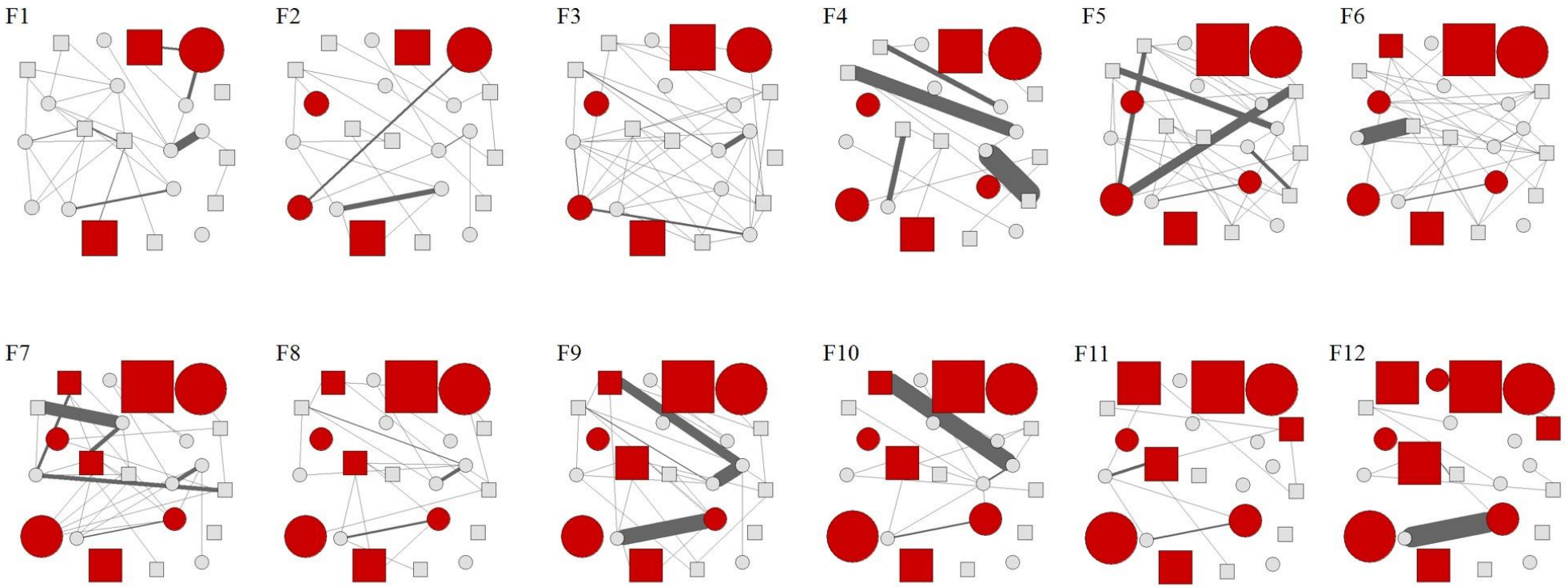
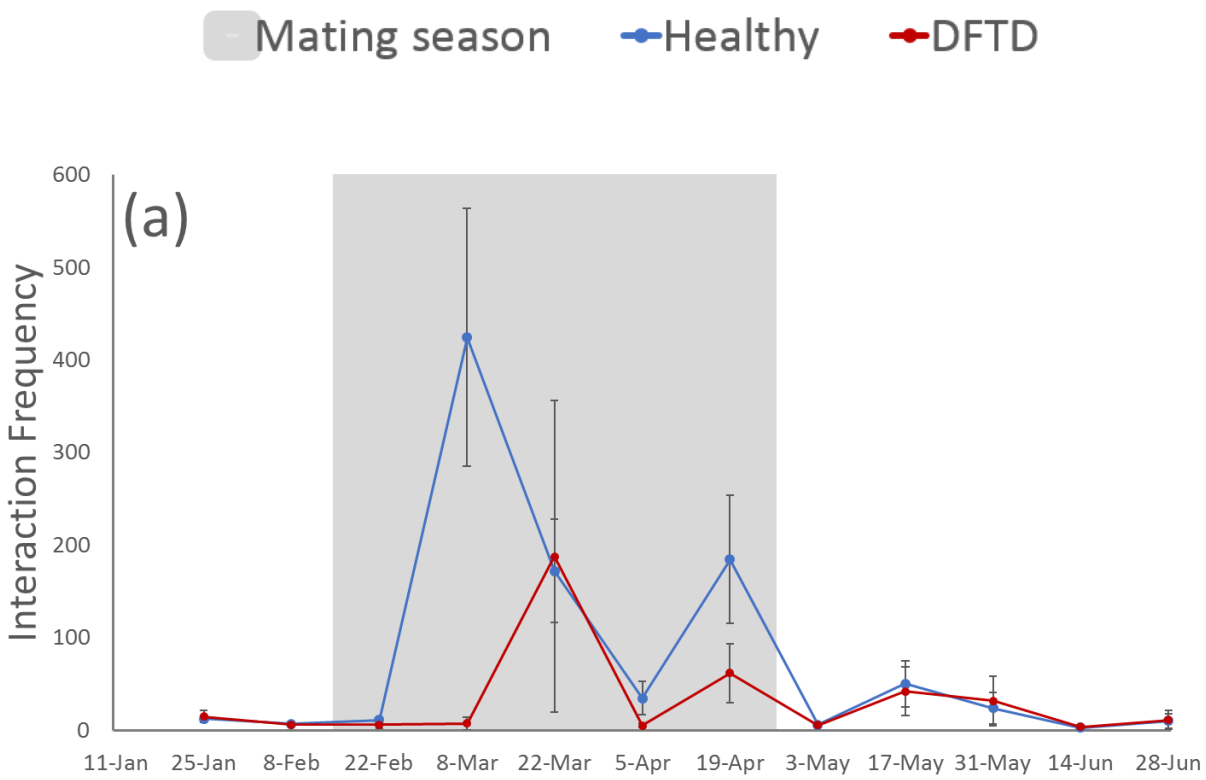
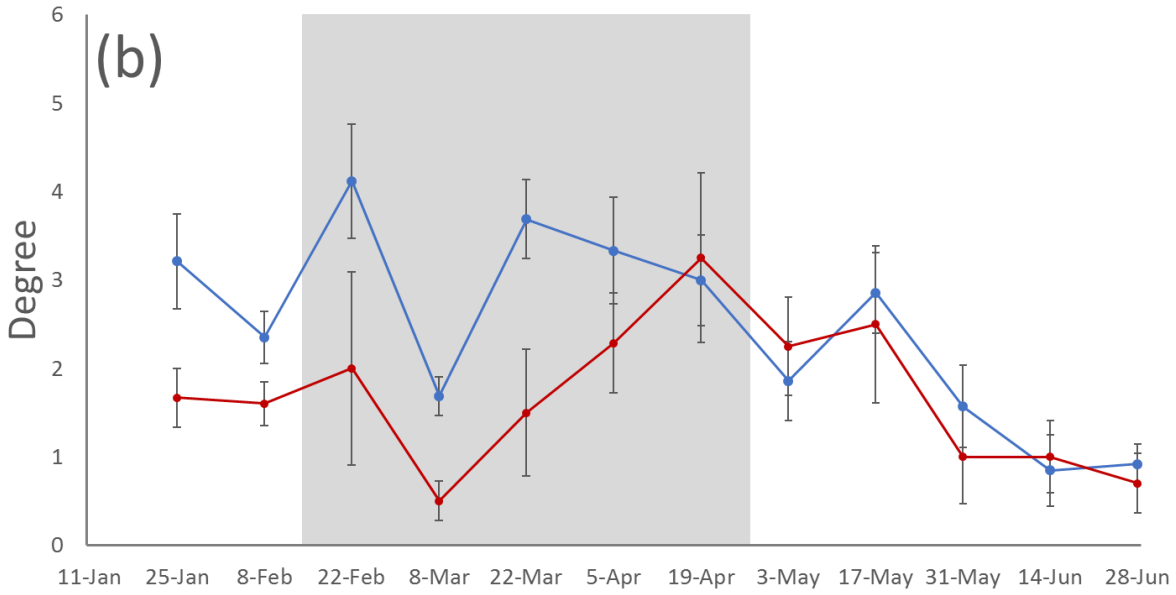
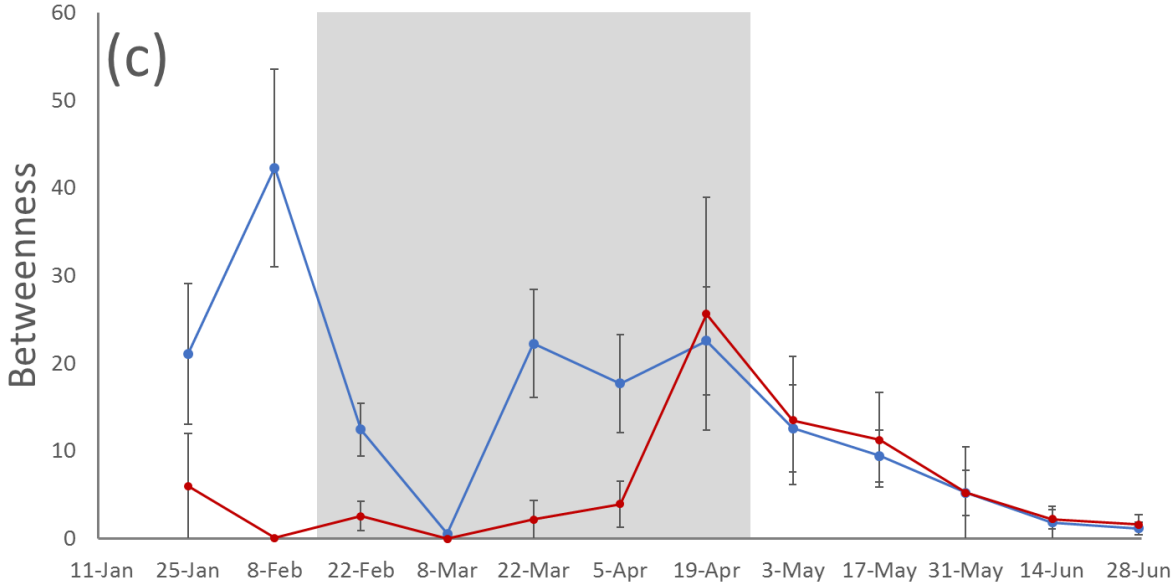
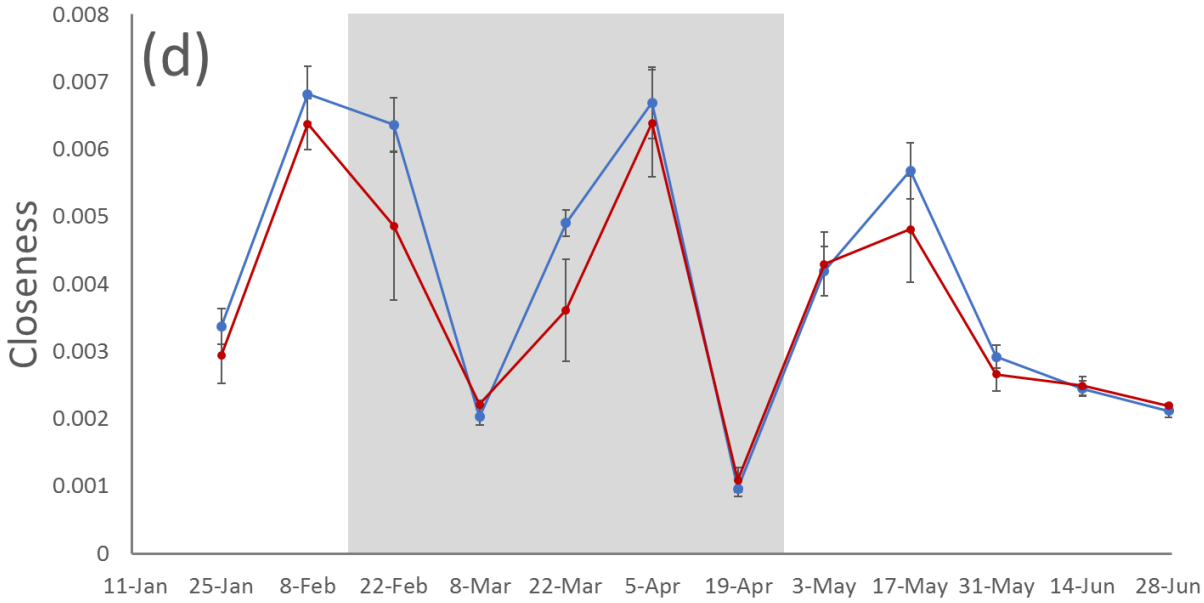


Figure 5.1 Fortnightly contact networks based on the interactions between individual Tasmanian devils over the course of six months during the early stages of a DFTD outbreak; F1 – 12 represent fortnightly time steps. Squares represent males, while circles represent females. Nodes coloured red represent those with clinical symptoms of DFTD, while size is based on tumour load (0 to > 200 cm^3). Edges between nodes represent number of interactions within the dyad, the thicker the line, the more interactions between those individuals.


Mating season
Healthy
DFTD
(a)
Interaction Frequency
600
500
400
300
200
100
0
11-Jan
25-Jan
8-Feb
22-Feb
8-Mar
22-Mar
5-Apr
19-Apr
3-May
17-May
31-May
14-Jun
28-Jun


(b)
Degree
6
5
4
3
2
1
0
11-Jan
25-Jan
8-Feb
22-Feb
8-Mar
22-Mar
5-Apr
19-Apr
3-May
17-May
31-May
14-Jun
28-Jun


(c)
Betweenness
60
50
40
30
20
10
0
11-Jan
25-Jan
8-Feb
22-Feb
8-Mar
22-Mar
5-Apr
19-Apr
3-May
17-May
31-May
14-Jun
28-Jun


(d)
Closeness
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0
11-Jan
25-Jan
8-Feb
22-Feb
8-Mar
22-Mar
5-Apr
19-Apr
3-May
17-May
31-May
14-Jun
28-Jun

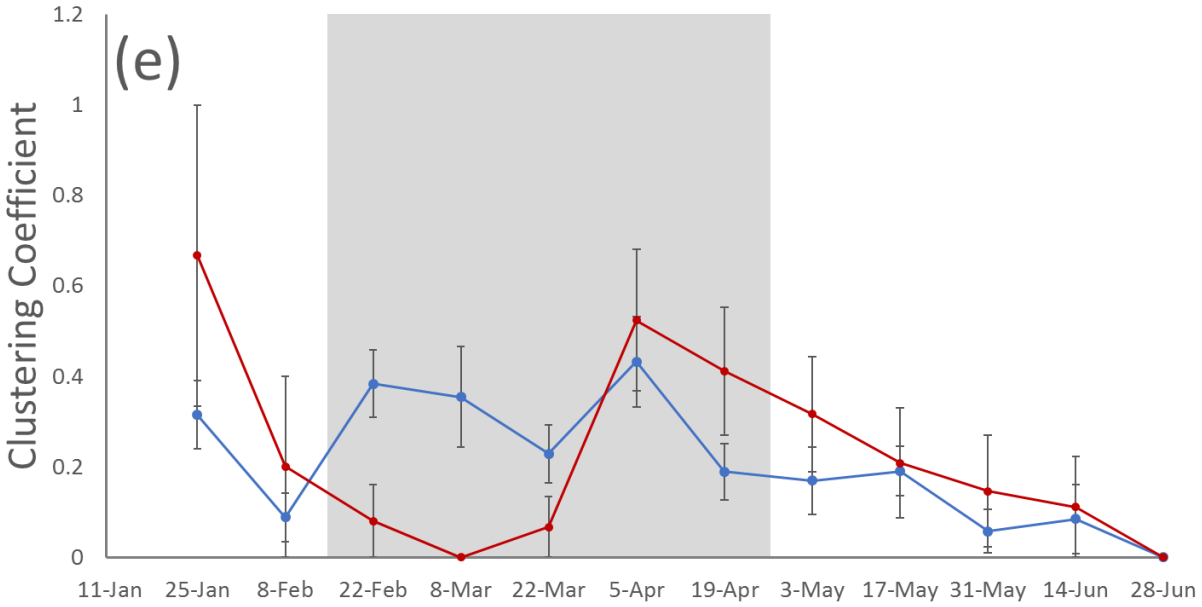


Figure 5.2 Mean network metrics of (a) interaction frequency, (b) degree, (c) betweenness, (d) closeness and (e) clustering coefficient through fortnightly contact networks for healthy devils (blue) and those with clinical symptoms of DFTD (red). The Tasmanian devil mating season is shaded in grey. Error bars indicate 95% confidence intervals – periods with non-overlapping error bars represent a significant effect of infection status in node-permuted significance tests.

TERGMs

The probability of edge formation in fortnightly contact networks was found to significantly decrease on infection with DFTD; this effect held across both the mating and non-mating seasons (Table 5.1a). Individuals with DFTD were predicted to be 28 % (C.I. = 19 – 75 %) less likely to form an edge with another individual in the network during the mating season (Table 5.1a) and 48 % (C.I. = 18 – 80 %) less likely during the non-mating season (Table 5.1a). Edges were also more likely (Mating season estimate = 1.73, C.I. = 1.55, 2.43; non-mating season estimate = 1.99, C.I. = 1.75, 2.30; Table 5.1a) to form with individuals a devil had shared an edge in the previous time period, indicating the persistence of regular interaction partners through time, regardless of infection status. There was no effect of sex or number of wounds accrued on the probability of edge formation, while sex-mixing was unbiased through time in both seasons (Table 5.1a).

The same patterns held in TERGMs investigating the effect of tumour load, with devils becoming progressively less likely to form edges with other individuals in the network, the higher their tumour load became (Table 5.1b). For each increasing level of category of tumour load (1 to 4) that an individual progressed through, the likelihood of forming an edge decreased by 17 % (C.I. = 5 – 30%) in the mating season, and by 15% in the non-mating season (C.I. = 5 – 25%; Table 5.1b).

a) DFTD status

Model term	*Mating Season*		*Non-mating Season*	
	Estimate	*C.I.*	*Estimate*	*C.I.*
Edges	**-2.49**	**-3.56, -1.62**	**-2.43**	**-2.98, -2.05**
Memory	**1.73**	**1.55, 2.43**	**1.99**	**1.75, 2.30**
Sex (M vs F)	0.28	-0.62, 0.86	0.04	-0.35, 0.34
Same Sex vs Different Sex	-0.06	-0.41, 0.19	-0.19	-0.63, 0.23
Wounds	0.08	-0.004, 0.18	0.11	-0.13, 0.18
DFTD status (+ ve vs. - ve)	**-0.28**	**-0.75, -0.19**	**-0.48**	**-0.80, -0.18**

b) Tumour load

Model term	*Mating Season*		*Non-mating Season*	
	Estimate	*C.I.*	*Estimate*	*C.I.*
Edges	**-2.78**	**-3.87, -1.88**	**-2.81**	**-3.30, -2.53**
Memory	**1.70**	**1.53, 2.40**	**2.02**	**1.78, 2.35**
Sex (M vs F)	0.29	-0.61, 0.87	0.07	-0.31, 0.40
Same Sex vs Different Sex	-0.05	-0.41, 0.18	-0.19	-0.63, 0.22
Wounds	0.08	-0.01, 0.17	0.09	-0.12, 0.20
Tumour Load (0 to 4)	**-0.17**	**-0.30, -0.05**	**-0.15**	**-0.25, -0.05**

Table 5.1 Model output for temporal exponential random graph models investigating the influence of a) DFTD status and b) tumour load on edge formation within fortnightly contact networks during the mating and non-mating seasons. Confidence intervals (C.I.) provide the lower and upper bounds of the 95% confidence interval around the model estimate. Significant terms are those for which the confidence intervals do not cross zero – these are highlighted in bold.

NAMs

None of the seasonal network metrics examined proved strong predictors of devil's disease status at the end of the study period (Table 5.2). There was no sex bias observed in final disease status, nor any effect of the number of wounds accrued during the mating or non-mating season. Additionally the non-significance of the *weightlag()* term indicates that individuals are not more likely to interact with other individuals of the same disease status (Table 5.2).

Mating season

Model term	Estimate	S. E.	Z value	P value
Intercept	0.594	0.270	2.200	0.045*
Sex	- 0.240	0.486	- 0.493	0.630
Wounds	0.048	0.048	1.007	0.331
Degree	- 0.0002	0.0005	- 0.354	0.723
Betweenness	0.014	0.020	0.736	0.474
Closeness	- 7.830	3.682	- 2.127	0.051
Clustering Coef.	- 0.514	1.894	- 0.271	0.790
Weightlag()	0.0007	0.0006	1.220	0.243

Non-mating season

Model term	Estimate	S. E.	Z value	P value
Intercept	0.716	0.294	2.435	0.029*
Sex	- 0.085	0.462	- 0.184	0.857
Wounds	0.002	0.071	0.030	0.976
Degree	0.0006	0.003	0.213	0.835
Betweenness	- 0.011	0.021	- 0.496	0.627
Closeness	- 0.489	4.542	- 0.108	0.916
Clustering Coef.	0.072	2.189	0.033	0.974
Weightlag()	- 0.003	0.003	- 0.884	0.392

Table 5.2 Model output of network autocorrelation models run on weighted mating and non-mating season Tasmanian devil networks. Models examined DFTD status at the end of the season as a function of individual sex, number of wounds received, and the network position measures of degree, betweenness, closeness and

clustering coefficient, while also controlling for the non-independence inherent in these measures.

DISCUSSION

Here we provide the first empirical study of the real-time spread and progression of a transmissible cancer through a population of Tasmanian devils by closely monitoring their disease status and interactions over a six-month period. Devil's probability of interaction reduces when they begin to display clinical signs of DFTD and this effect amplifies with increasing tumour load. There are then consequent alterations in the position DFTD infected animals occupy within their social network, particularly during the mating season when most potential disease transmission opportunities (in the form of injurious biting) occur. Conversely, the network position of healthy animals had no clear influence on their likelihood of developing clinical signs of DFTD in the short-term. These findings have implications for our understanding of how DFTD affects Tasmanian devils at both the individual and population levels, while also contributing to our knowledge of cancer-induced sickness behaviours.

The probability of devils interacting within their social network reduced significantly as they began to display clinical signs of DFTD, further reducing as tumour load increased. This is in line with expectations that infected devils would reduce their interactions as the cost of infection became higher. Devils with higher tumour load appear to become increasingly socially isolated, which can be a consequence of both the metabolic and physiological costs of the cancer. Given that the majority of interactions within this species are based around competition (for food or mates), a decrease in interactions is also likely to signal a reduced ability to compete. A decline

in competitive ability is expected to align with increased tumour load as the condition of infected individuals has a tendency to decrease as tumour load increases (Ruiz-Aravena et al. 2018). Specifically, Ruiz-Aravena et al. (2018) found that body condition in DFTD infected devils declines sharply as tumour volume progresses from medium to large loads (particularly in males). Given that our data also indicates a decrease in interaction rate, particularly at high tumour volumes, there could be a threshold beyond which the effect of sickness behaviour becomes more pronounced. Reduced interaction rates and network connectivity of devils in the latter stages of DFTD infection has consequences for predicted transmission dynamics of the disease. The point at which devils would be expected to be most liable to transmit disease to new hosts is when tumours are at their largest. This is when they are most likely to either be the target of bites by healthy devils or deliver large doses of tumour cells via biting (Pearse and Swift 2006; Obendorf and McGlashan 2008). We show that devils with high tumour loads interact with other animals infrequently, which reduces their potential as DFTD vectors. Instead, interaction patterns suggest it may be devils in earlier stages of infection, with smaller tumour loads but suffering less from the effects of the disease in terms of overall health, condition and sickness behaviour, that are likely to be driving disease transmission.

Interaction patterns alter significantly in individuals carrying DFTD, a tendency which has measurable negative effects on their social network position. The observed effects are driven by reproductive season, with most network metrics aligning in the non-mating season but diverging during the mating season. Notably, the interaction rates and network metrics of DFTD-infected devils were more similar to those of healthy individuals towards the end of the mating season. Healthy male devils have

likely already been involved in lengthy mating interactions by this stage (unlike the infected individuals), and this may cause a drop in healthy devil body condition (Boonstra 2005). Lengthy mating interactions result in reduced condition, low energy levels and compromised immune function in dasyurids (McDonald et al. 1986; Dickman and Braithwaite 1992). The subsequent reduced late-mating season influence of DFTD on network position may result from two effects. Firstly. DFTD-infected devils are likely to be more competitive for resources later in the mating season, when healthy individuals are in poor condition. Secondly, if any avoidance behaviour is occurring on the part of healthy animals, their poor condition and requirement for sustenance may now outweigh the potential costs of interacting with an infected individual. Thus, there is an increase in connectivity of diseased individuals as the mating season comes to a close - both in terms of the number of individuals they interact with and whether they occupy key positions capable of reaching disparate parts of the network. This period consequently may be important to transmission dynamics of the disease. Not only are DFTD vectors involved in more interactions, those interactions are with animals which are already likely to be in poor condition and immunocompromised, making them particularly vulnerable to infection. While mating season interactions have been identified as very important to DFTD transmission previously (Hamede et al. 2013; Hamilton et al. 2019), our results indicate that late-season interactions may be critical for transmission.

It remains difficult to disentangle the potential effects of sickness behaviours from the possibility that healthy devils are actively avoiding those with DFTD. Avoidance behaviour could become particularly pronounced as tumours increase in size and present an increasingly clear visual signal that the host is carrying disease. However,

large tumours might also exacerbate sickness behaviour. DFTD infection is also associated with olfactory cues, with ulcerated tumours regularly the source of secondary infections. Devils have a keen sense of smell (Rose et al. 2017), so it is likely that they react to DFTD olfactory cues, although whether they alter their behaviour towards conspecifics based on these cues is unknown. Our results suggest that healthy individuals are not avoiding diseased individuals entirely. First, networks are not segregated into healthy and DFTD-infected subgroups (see Table 5.2). Second, there are long-term associations within the contact networks which continue to persist when one half of a dyad becomes symptomatic. This is demonstrated by female-female relationships that persisted through the entire six-month study period, including after one female began to develop clinical signs of DFTD. Most of these dyadic interactions took place during the day, indicating the females were regularly denning together; a behaviour unlikely to result in competitive interactions or injury (Hamilton et al. 2019). These interactions persist after infection, which indicates that in these cases, healthy individuals are not actively avoiding symptomatic individuals. While we cannot rule out behavioural avoidance, it is unlikely to be the sole driver of the alterations in interaction patterns observed in individuals with DFTD.

There is growing evidence that the effects of infection can be sex-specific, whereby females both bear greater costs of infection (Akinyi et al. 2019) and an improved ability to combat or survive aggressive diseases like cancer (OuYang et al. 2015; Radkiewicz et al. 2017). In Tasmanian devils, females are more tolerant to the progression of DFTD (Ruiz-Aravena et al. 2018) and have higher survival (Margres et al. 2018). Additionally, the physiological effects of DFTD are likely to vary between the sexes, particularly when it comes to mating interactions. Infection will have

additional physiological effects on female devils during the reproductive period, the delay of oestrus for example (Hesterman et al. 2008b), which could affect the timing of their mating interactions. Conversely, male mating behaviour is unlikely to be affected physiologically by DFTD – spermatogenesis occurs over an extended period in devils, so should not be suppressed to any great degree by infection (Hesterman and Jones 2009). Any mating season effects on males will therefore be driven by voluntary (as opposed to physiologically driven) behaviour, with males likely to be the instigators of mating interactions with females. Given the different pressures infection places on males and females, sex differences may translate to divergences in DFTD-induced behavioural adjustments in the species. While there were no effects of sex on interaction rates or network position overall, this may alter if DFTD-infected individuals could be further sub-divided by sex. Unfortunately, we were unable to test for sex differences in the current study due to restrictively small sample sizes once the population was split by both DFTD status and sex. The potential for sex-based differences in sickness behaviour is worth examining in future studies, as it may have implications for both mate choice and transmission dynamics of the disease.

Evaluating cancer-induced effects on behaviour is rare in wildlife studies, owing to the difficulty of diagnosis in a wild setting. Here we provide evidence that progression of cancer alters interaction rates and position within a social network in Tasmanian devils. This has implications for our understanding of how this widespread disease may affect devils, and other species more broadly. Additionally, the assessment of how the increasing burden of cancer infection affects individual devils adds to our knowledge of the impacts of such a ubiquitous disease on wildlife behaviour. Improved knowledge of the side-effects of cancer can help with understanding the

overall effects of oncogenic phenomena in wildlife across taxa and assess its often overlooked effects on behaviour.

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Chapter 6

General Discussion: Research summary, implications and future work

Research summary

Behaviour is critical to our understanding of the Tasmanian devil – DFTD system, and it provides a central theme running through this thesis (see Figure 1). While the initial cause of DFTD was a cellular abnormality, the behavioural system into which it emerged inarguably facilitated transmission of the disease, as well as its persistence. As evidenced through population level patterns, Tasmanian devil behaviour appears to be responsive to the selective pressure of DFTD (Figure 6.1a). A devil's behaviour, in terms of the way it interacts with other individuals, influences the number of bite wounds it receives (Figure 6.1b). The number of bite wounds received directly affects a devil's likelihood of being involved in a DFTD transmission event (Figure 6.1d), and hence developing the disease in the future. Once the disease has been acquired, the host's interaction tendencies alter (Figure 6.1a), with clear repercussions for its involvement in the ongoing transmission process (Figure 6.1d). This transmission process can be modelled using our understanding of how behaviour and bite wounds interact to create predictors of disease spread (Figure 6.1c), furthering our knowledge of key epidemiological parameters. The dynamics occurring between devils and DFTD highlight the importance of measuring behavioural and interaction heterogeneities, in addition to how they alter with season and demography. Studying how behaviour and interactions influence the transmission process can facilitate our understanding of epidemiology and help refine models of disease dynamics.

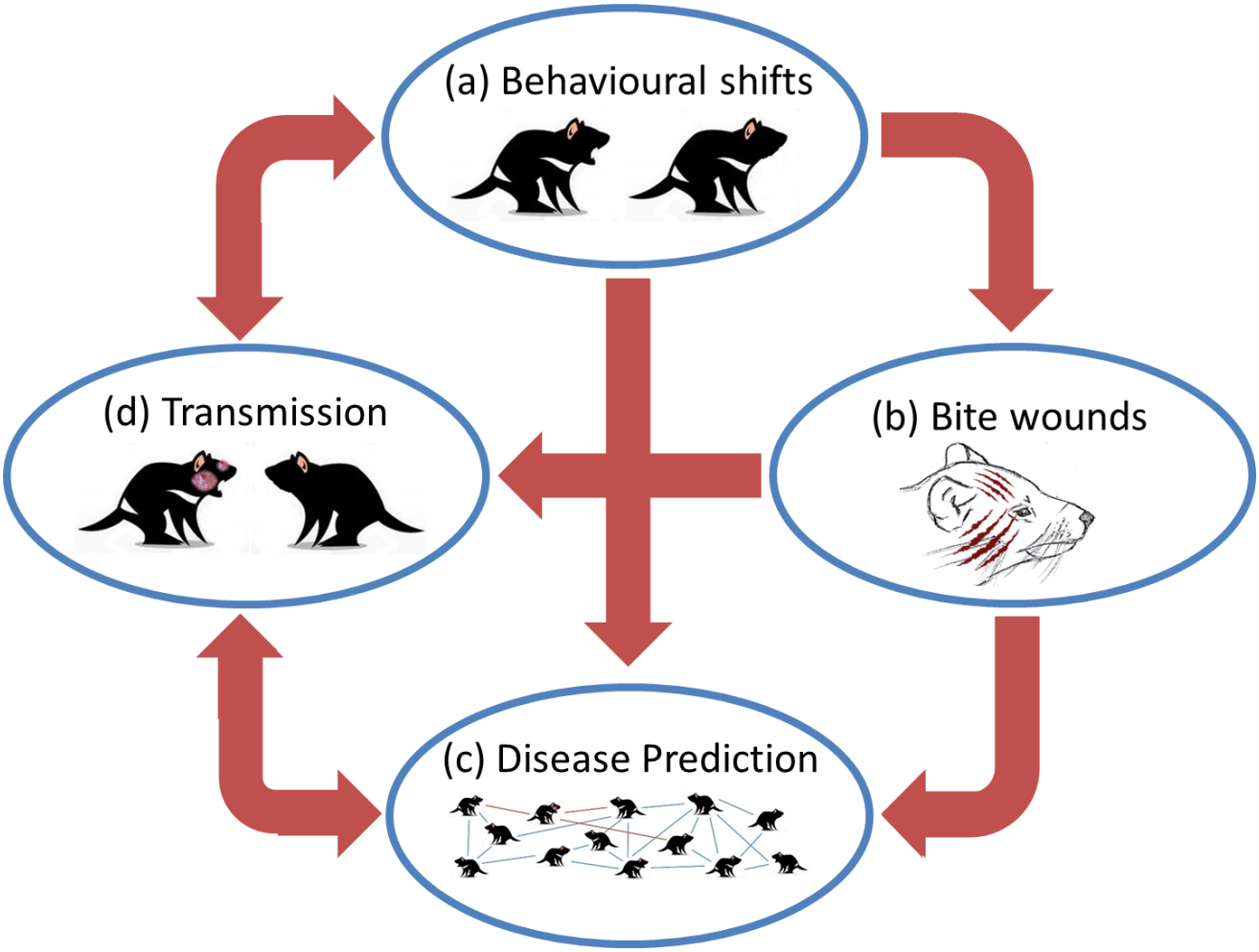

Figure 6.1 Flow diagram depicting how the central themes presented in this thesis flow into one another and help further our understanding of DFTD.

How devils are reacting in the face of the threat of DFTD is ultimately shaped by the nature of their interactions, and their behavioural response to both interactions with diseased individuals and following acquisition of the disease itself. With the results collated here, we can begin to unpack the factors that are playing a role in the devil's ongoing behavioural adaptation to DFTD.

The devil's in the detail

The position of individual Tasmanian devils within their social network does not appear to be a strong driver of susceptibility to DFTD or the transmission process more broadly. In many other systems, network position has been found to have important consequences for future probability of infection, or likelihood of playing a facilitative role in the transmission process (Krause et al. 2014). For example, in African lion (*Panthera leo*) networks small numbers of highly connected individuals have a disproportionate effect on transmission dynamics (Craft et al. 2011), while in house mice (*Mus musculus domesticus*) alterations in the network connectivity of infected individuals can constrain epidemics of bacterial infection considerably (Lopes et al. 2016). Conversely, Tasmanian devil social networks have been examined on three separate occasions (Hamede et al. 2009; Hamilton et al. 2019; Chapter 5 – Hamilton et al. *in prep*), with network position found to exert little influence on the likelihood of involvement in potential transmission events. A broader consistent pattern observed was the role of overall network structure in population susceptibility to DFTD, with networks found to comprise one large component in each study. Such structures present a pathway for DFTD to spread through local populations over time without over-reliance on keystone individuals providing bridges between disparate sections of the network. While the role of individual network position has reduced importance, the context of individual's interactions within the network have significant consequences. Mating interactions appear to be particularly important to the DFTD transmission process – the strongly driven, actively sought nature of these interactions means they occur regardless of network structure. This aligns with our knowledge of DFTD transmission dynamics, which resemble those of a sexually transmitted infection (McCallum et al. 2009), i.e. they are density independent, allowing persistence and a retained prevalence even at low population numbers. However, from modelling of disease dynamics based on devil networks it is clear that mating season

interactions alone are not sufficient to sustain long-term DFTD persistence. Consequently, we might predict that as interaction density in devil social networks reduces as populations decline over time, aggressive non-mating season interactions may grow to play more of a role in persistence of the disease through generations. Alternatively, the fact that the mating season elongates as higher proportions of females begin to breed precocially in DFTD-affected populations (Jones et al. 2008), may be critical not only to long-term survival of devils but ongoing persistence of the disease. Potential temporal shifts in network structure as disease takes hold are worthy of further study to help understand how DFTD persists in devil populations over long timeframes.

There are multiple examples in the devil-DFTD system of how males and females are impacted differently by the dynamics of the disease (Lachish et al. 2011; Margres et al. 2018; Ruiz-Aravena et al. 2018; Hamilton et al. 2019). Infection will confer different selective pressures on each sex, both physiologically and behaviourally, because of fundamental differences in reproductive demands. For infected females, there is likely to be a seasonally driven element to behavioural alterations, dependent on the reproductive phase the female is in when clinical symptoms manifest. For example, a female with late-stage dependent young is likely to respond differently to infection than a pre-reproductive female, meaning the two may have divergent roles in disease spread. Infected males are likely to be driven to pursue reproductive opportunities even as their condition declines (a well-studied life history trait in male dasyurids; Dickman and Braithwaite 1992; Bradley 2003), affecting their role in ongoing transmission dynamics. Additionally, males are involved in more potential transmission events (Hamilton et al. 2019), giving individual infected males a higher probability of drawing multiple others (predominantly females) into the transmission cycle. The fact that biological divergences in selective pressures exist, alongside a lack of detectable

sex-bias in infection rates, suggests that the sexes impact transmission dynamics differently but both are important to the overall process.

The primary focus of this thesis has been to evaluate how behaviour affects infection at the level of the host, the Tasmanian devil. However, it is also worth considering the connotations that behaviour and its potential shifts have for the pathogen that devils are harbouring, the tumour itself. Devils and facial tumour lineages are effectively locked in an evolutionary arms race, with both showing signs of adaptation over short evolutionary time-scales (Pearse et al. 2012; Hamede et al. 2015; Epstein et al. 2016; Hohenlohe et al. 2019). There are behavioural alterations which will be of benefit to devil fitness, and those which will enhance further transmission of the tumour. The two are not necessarily mutually exclusive. For example, while an increase in aggressive behaviour may enhance tumour transmission and decrease devil fitness in the short term, in the longer term an overtly aggressive devil population is likely to be wiped out – a negative outcome for both devil and tumour. How both host and pathogen benefit from particular behaviours, and whether there is a point at which coexistence is a likely outcome, is worth working towards understanding.

How Tasmanian devils continue to adapt in the face of DFTD will affect our approach to their ongoing management. In the future, the Tasmanian devils that have adapted to coexist with their facial cancer are likely to be behaviourally distinct to those observed in both disease-free and insurance/captive populations. Patterns of behavioural change are important to take under consideration when planning future management strategies towards devil conservation. Additionally, the Tasmanian devil system can provide lessons about behavioural adaptation and evolution in the face of disease outbreaks.

The detail from the devils

Moving beyond Tasmanian devils, this system has a lot to teach us about the interface of behaviour and disease, and the influences they can have on one another. For a process so integral to disease transmission, behaviour has only relatively recently begun to be studied in detail in disease ecology (Han and Ostfeld 2019). In particular, the role of behavioural adaptation as a disease avoidance mechanism is worthy of further study. Emphasis is often concentrated on how physiological mechanisms can allow organisms to adapt upon infection. These generally involve either developing resistance to a pathogen, through alterations in the immune system, or tolerance via physiological and immunological adaptations over time to bear the increased fitness costs of infection (Schneider and Ayres 2008). Both of these mechanisms involve adaptation consequent to contracting a pathogen. Behavioural avoidance, however, involves never being exposed to infection – selection pressure will become apparent rapidly as individuals unable to avoid infection will suffer fitness consequences. From a population perspective, avoidance thus represents the most expedient, and effective way to cope with a disease outbreak. Despite having one of the strongest effects on disease dynamics, avoidance is often overlooked. There remains a diversity of systems in which avoidance of infection is of interest to understanding disease dynamics. For example, avoidance of white-nose syndrome infection by a proportion of individuals plays a role in colony persistence in bats (Cheng et al. 2019), but the mechanics of this avoidance are currently unclear. In species of conservation concern affected by disease, pinpointing the traits of individuals likely to avoid infection is important for management initiatives (e.g. African wild dogs, *Lycaon pictus* – Canning et al. 2019; echo parakeets, *Psittacula eques* – Tollington et al. 2019; eastern gorillas, *Gorilla beringei* spp. – Porter et al. 2019). Further studies of behavioural adaptations in the face of infection can facilitate our understanding of both short and long-term effects of infection on wild populations.

Social network analysis has significantly contributed to the field of disease ecology in recent years, highlighting how disease can move through populations and the role individuals can play in this process. However, the devil-DFTD system illustrates how, in some cases, the context of interactions within a network can be more important than the structure of the network itself. In devils, a high proportion of close-range interactions are completely benign from a disease transmission perspective. This is likely to be the case in a host of other systems which require close contact for transmission – differentiating networks based on interaction context can help parameterise models more accurately. Disentangling different network types is a challenging process, but one that has begun to be attempted (Duboscq et al. 2016; Kulahci et al. 2018; Silk et al. 2018). Further refinement of this process, in addition to identifying the contexts of contacts important to disease transmission in different host-pathogen systems, is key to future studies of wildlife diseases.

Studying how behaviour influences disease dynamics has wider implications, with the potential to study how evolution acts on their interplay. This is particularly pertinent in the case of cancer, a disease common to all walks of biological life but challenging to study the effects of. Recent studies have shown that individuals at different stages of cancer progression significantly alter their social behaviour, and that social behaviour can actually impact tumour growth itself (Dawson et al. 2018). Cases where cancer is externally diagnosable are rare, so knowledge of the impact of cancer on wild animals is limited. Tasmanian devils represent an interesting opportunity to further investigate cancer-mediated evolution in a wild setting. By studying interactions of devils in a population recently infected with DFTD, I have already shown that cancer progression impacts social behaviour in these animals. Further studies will help to elucidate how behavioural changes may alter the evolution of both tumours and devils.

Future directions

Ongoing research into Tasmanian devils is an area with many avenues worth exploring, furthering our knowledge of this host-pathogen system, disease ecology and evolution more broadly. While devil networks have now been studied both pre- and shortly post-DFTD infection, the ongoing effects of DFTD on network structure and interaction dynamics remain unknown. Based on previous findings, we can hypothesise that alterations in network structure due to declining devil density will have little impact on overall transmission dynamics, but this may prove unfounded. Dramatic alterations in the way devils interact, or in their behavioural tendencies over time, have the potential to affect network structure to the degree that ongoing disease spread may be impacted.

In a similar vein, a more challenging but informative facet to explore is landscape level network dynamics. Study of local networks is of keen interest, but we have very little understanding of how DFTD moves between populations at the wider level. Inter-population interactions are vital to disease spread in well studied systems (Drewe 2010; Craft et al. 2011; Weber et al. 2013), and identifying the individuals responsible for transmitting DFTD between populations would be of great assistance to ongoing management of the disease. These individuals are those with high betweenness that are conspicuous by their absence at the local scale but will be important to facilitating connectivity at the landscape scale. Additionally, the role of landscape heterogeneity and its influence on local density and movements, as well as the connectivity of populations across landscapes, is relevant to wider scale disease dynamics, but remains currently unexplored.

Better understanding the role of avoidance in this system will also be assisted by studying devil movement in tandem with their interaction patterns. From currently available data we know when two devils are interacting but are unaware of when individuals are within close range but avoid interaction. These incidences are of interest, as they would indicate a form of avoidance behaviour. Combining proximity logger technology with GPS capabilities (as has been achieved in the badger-bovine tuberculosis system; Woodroffe et al. 2016) will allow interaction and movement data to be combined, while also shedding light on the landscape connectivity mentioned above. Avoidance behaviour may be critical to understanding which devils within interconnected populations are able to avoid infection, and how their behaviour facilitates this. Knowledge of the role of behaviour in transmission dynamics would also be aided by further study of how handling behaviour correlates with likelihood of DFTD infection in the short- and long-term, and whether it can be linked to display of particular behaviours in a wild setting.

Tasmanian devils are showing extraordinary resilience to persist in the face of a unique threat. Exploring the behavioural aspects of that resilience has allowed us to visualise how devils may continue to adapt into the future. Letting evolution take its course, studying its processes along the way, is the best way to ensure their continued survival while furthering our knowledge of disease ecology, evolution and well-guided conservation practices.

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“Better the devil you know, than the devil you don’t…”